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For the Study of the Circulation

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American Heart Journal

VOL. 23 JUNE, 1942 NO. 6

Original Communications

THE CLINICAL FEATURES OF TRICUSPID STENOSIS

A STUDY OF TRIVALVULAR STENOSIS

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THE accuracy of diagnosis of valvular disease has improved greatly in recent years. The introduction of electrocardiography, although contributing mainly to our knowledge of coronary artery and myocardial disease, has indirectly aided in the diagnosis of valvular disease. The presence of right or left axis deviation has occasionally been the clue that has led to the recognition of a valvular lesion that otherwise might have been overlooked. The peculiar form of the P wave in some cases of mitral stenosis at times serves to identify this lesion when other methods leave one in doubt. The greater interest that has been taken in x-ray examination of the heart has also thrown considerable light on the diagnosis of valvular disease. Not only the correlation between the configuration of the cardiac silhouette and the post-mortem findings, but also fluoroscopic examinations have established certain general patterns that more or less correspond to specific types of valvular disease. Of even greater roentgenologic importance is the detection of calcification of the valves of the heart by fluoroscopic examination.[1] Apart from all of this, bedside methods of inspection, palpation, auscultation, and percussion have become more precise. The result has been that a well-trained clinician is able to make a fairly accurate diagnosis of the anatomic condition of the valves in most cases.

Mitral stenosis, the most important of the valvular defects, is also the defect diagnosed most accurately. Aortic valvular disease, particularly aortic stenosis, has only recently been recognized as a common lesion, and methods of its detection are becoming more clearly understood. It is still too frequently overlooked, but at present it is fair to

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TABLE I

CASE NO.	AGE AT DEATH (YEARS)	SEX	DURATION OF RHEUMATIC HISTORY (YEARS)	DURATION OF FAILURE (YEARS)	HEPATIC ENLARGEMENT*	RHYTHM	AXIS DEV.	P-WAVE CHANGES	TRICUSPID STENOSIS*	MITRAL STENOSIS*	AORTIC STENOSIS*
Marked Tricuspid Stenosis											
1	40	F	31	23.0	3	A.F.	R.A.D.	A.F.	3	3	0
2	36	F	30	3.5	0	Flutter	R.A.D.	Flutter	3	3	1
3	39	F	25	7.0	1	A.F.	R.A.D.	A.F.	3	3	2
4	20	F	17	0.2	3	Reg.	R.A.D.	Broad, flat	3	3	2
5	45	F	36	3.0	3	A.F.	R.A.D.	A.F.	3	3	3
6	32	F	11	5.5	3	Reg.—A.F.	R.A.D.	Broad, flat, notched	3	3	3
7	17	F	9	0.5	3	Reg.	?	?	3	3	2
8	21	F	12	3.5	3	A.F.	R.A.D.	A.F.	3	3	2
9	27	F	9	2.5	1	Reg.	?	?	3	3	2
10	45	F	30	8.0	3	A.F.	?	?	3	3	3
11	36	F	?	15.0	3	A.F.	R.A.D.	A.F.	3	3	3
Av.	32.5		21.0	6.5	2.4				3.0	3.0	2.1
Moderate Tricuspid Stenosis											
12	38	F	19	12.0	0	Reg.	None	Low, broad, flat	2	2	2
13	43	F	10	8.0	3	A.F.	R.A.D.	A.F.	2	3	0
14	24	M	14	20.0	2	Reg.	R.A.D.	Small, flat, notched	2	3	1
15	23	M	10	1.5	3	Reg.	R.A.D.	Coarsely notched	2	3	2
16	43	F	29	1.0	3	A.F.	R.A.D.	A.F.	2	3	3
17	51	F	43	4.0	1	A.F.	None	A.F.	2	3	3
18	44	M	21	18.0	2	A.F.	R.A.D.	A.F.	2	3	3
19	27	F	15	10.0	2	Reg.	?	?	2	3	2
20	39	F	17	10.0	3	A.F.	R.A.D.	A.F.	2	3	1
21	18	M	10	4.0	3	Reg.—A.F.	?	?	2	3	0
22	38	F	30	3.0	1	Reg.	?	?	2	3	2
Av.	35.2		19.8	8.3	2.1				2.0	2.9	1.7

Slight Tricuspid Stenosis											
23	32	M	10	0.3	3	Reg.	L.A.D.	Broad, flat, notched	1	2	0
24	38	M	20	0.5	0	Reg.	R.A.D.	Flat top, notched	1	2	0
25	39	F	30	19.0	2	A.F.	R.A.D.	A.F.	1	2	0
26	47	F	24	14.0	3	Reg.	None	Broad, flat, notched	1	2	2
27	51	F	47	15.0	3	A.F.	R.A.D.	A.F.	1	2	2
28	26	F	16	16.0	3	Flutter	R.A.D.	Flutter	1	3	0
29	27	M	7	0.0	3	A.F.	R.A.D.	A.F.	1	3	0
30	48	M	30	1.5	2	Reg.	R.A.D.	Sharp, notched	1	3	1
31	26	M	5	1.5	3	Reg.—A.F.	R.A.D.	Broad, flat, notched	1	3	2
32	24	F	21	5.0	1	Reg.	R.A.D.	Broad, flat, notched	1	3	3
Av.	35.8		21.0	8.1	2.3				1.0	2.5	1.0
Entire Group (32 Cases)											
Av.	34.3		20.8	7.4	2.3				2.0	2.8	1.6

*1 = slight; 2 = moderate; 3 = marked.

say that, unless the patient is moribund, aortic stenosis can be recognized in the majority of cases. The lesion that has so far defied clinical recognition is organic tricuspid valvular disease, either stenosis or insufficiency. That organic involvement of this valve is by no means rare will become clear from the results of this present study. We are aware of no published communication which indicates that the antemortem diagnosis of tricuspid valvular disease is being made with any degree of accuracy comparable to that which obtains in the diagnosis of aortic or mitral disease. In fact, the experience has been that most cases of tricuspid stenosis are first recognized at the autopsy table.

There is at present no satisfactory sign or symptom that characterizes organic tricuspid disease. The systolic pulsation of the veins in the neck, or even of the liver, has long been recognized as evidence of incompetency and regurgitation of the tricuspid valve. Tricuspid insufficiency, however, not infrequently results when the heart is dilated and the tricuspid valve is relatively incompetent whether organic valvular disease is present or not. In other words, tricuspid insufficiency is not synonymous with tricuspid endocarditis. An elevated venous pressure, although common, if not invariable, in tricuspid stenosis, is present whenever there is right-sided failure or venous obstruction of the heart irrespective of the underlying cause. Large, distended jugular or temporal veins, although suggestive of tricuspid involvement, may be present without this lesion. Systolic pulsations of the liver have often been looked upon as evidence of tricuspid disease, but at times it is difficult to elicit this sign, as the movements of the liver may be due to direct impact from the adjacent aorta or heart. It is of more value when, on bimanual palpation, the liver can be actually felt to expand so that simultaneously a forward movement may be made out with one hand and a backward movement with the other. This merely indicates that there is tricuspid insufficiency. There have been occasions when prominent auricular waves could be detected in polygraphic tracings taken in the region of the liver. Likewise prominent auricular waves in jugular tracings have been described as occurring in tricuspid stenosis.

Little progress has been made in the interpretation of murmurs that might identify this lesion. One would expect to find systolic or diastolic murmurs in the tricuspid area, just as similar murmurs are heard at the apex in the case of mitral stenosis. The difficulty is that practically all cases of tricuspid stenosis have accompanying mitral stenosis, and many have aortic stenosis as well. Because the mitral and tricuspid valves are situated in close proximity, and the resultant murmurs can be of the same time and character, interpretation of auscultatory findings will always be difficult and confusing. Some of the older clinicians have called attention to the peculiar olive discoloration of the skin associated with tricuspid disease. One would predict that, just as the left auricle dilates with mitral stenosis, the right would dilate with

tricuspid stenosis. This evidence ought to be detectable on x-ray examination. Finally, the only information which electrocardiography could possibly furnish that might directly result from the tricuspid lesion would be evidence of right auricular dilatation and hypertrophy. Right axis deviation, if present, results from the mitral stenosis that coexists, for the right ventricle becomes enlarged not from the tricuspid, but from the mitral stenosis. Other clinical findings, such as undue cyanosis and polycythemia, have been thought to accompany tricuspid disease, but the fact that the diagnosis is rarely made with accuracy is sufficient evidence that none of the above criteria are diagnostically reliable. This study was therefore undertaken with the purpose of throwing some light on the diagnostic criteria and the clinical features that might aid in the recognition of organic tricuspid valvular disease.

The records of the pathologic department of the Peter Bent Brigham Hospital from 1913 to 1940 inclusive were analyzed. In a total of 4,437 autopsies 340 cases of rheumatic valvular disease, i.e., an incidence of 7.7 per cent, and 227 cases of mitral stenosis were found. Among these there were thirty-two cases of definite tricuspid stenosis, i.e., 9.4 per cent of all chronic rheumatic valvular disease. The degree of stenosis was regarded as marked in eleven, moderate in eleven, and slight in ten cases (Table I). Every case had an associated mitral stenosis. In addition there were sixty cases in which the tricuspid valve showed definite evidence of structural organic involvement (17.6 per cent of all chronic rheumatic valvular disease), most of which had a functional insufficiency of the tricuspid valve; some may have had a slight degree of stenosis, but not sufficient to be certain. If both groups are considered, it is apparent that 27.0 per cent of all cases of chronic rheumatic valvular disease have some form of tricuspid involvement. Organic tricuspid disease, stenosis or insufficiency, therefore, cannot be a rare condition.

CLINICAL CONSIDERATIONS

The average age at the time of death for the entire group of thirty-two cases was 34.3 years. There were nine males and twenty-three females. The preponderance of females is in accord with similar findings in cases with mitral stenosis in general.[2] It is of interest that there were no males in the cases of marked tricuspid stenosis.

There was a history of rheumatic fever or chorea in twenty-five of the thirty-two cases (78 per cent). Fifteen had rheumatic fever without chorea, and two had chorea without rheumatic fever; the remaining eight had both. There were seven that had neither rheumatic fever nor chorea. Many of the patients had more than one attack of rheumatic infection. Recurrences of such attacks, however, had no influence on the severity of the valvular lesion. In fact, the reverse seemed to be true, inasmuch as the incidence of frequent bouts of rheumatic fever

or chorea was much greater in those with slight tricuspid stenosis than in those with a higher degree of stenosis. Although scarlet fever is related to valvular disease only in so far as it may initiate an attack of rheumatic fever, it is of interest that six of the patients had a past history of scarlet fever; three of these had an additional history of rheumatic infection. The interval that elapsed between the first rheumatic infection and death averaged 20.6 years. There was no difference in this interval when the various degrees of tricuspid stenosis were compared.

The Wassermann reaction was positive in only one case, and in that instance there was both syphilitic disease of the aorta and rheumatic disease of the valves. The average blood pressure of these cases was 121/74 mm. and showed no appreciable variation in the three different degrees of stenosis of the tricuspid valve. Significant hypertension was infrequent in the entire group, for there were only two cases in which the systolic pressure was over 150 mm. (160 and 165), and three others with diastolic readings between 100 and 110 mm. in which the systolic pressures were below 140 mm.

The duration of congestive failure was an important part of this investigation because our original concept was that tricuspid stenosis seemed to protect the pulmonary circuit and delay the development of pulmonary congestion, that otherwise may progress rapidly in cases of mitral stenosis. When the cases in this study were analyzed from this point of view, it was found that the average duration of life after the first appearance of congestive heart failure (enlarged liver, ascites, pitting edema, basal râles or significant breathlessness) was 7.4 years. As has been shown in a previous communication,[3] this is considerably longer than for cases of pure aortic stenosis, pure mitral stenosis and combined aortic and mitral stenosis. In that study the duration of congestive failure was found to be 1.4 years in pure aortic stenosis, 2.9 years in pure mitral stenosis and 3.5 years in combined aortic and mitral stenosis. Further analysis showed that the duration was distinctly longer for those with moderate than those with marked tricuspid stenosis (8.3 and 6.5 years, respectively). The effect of aortic or mitral involvement in these cases of tricuspid stenosis was also investigated. In the twenty-four cases with some degree of aortic stenosis the duration of symptoms was 6.5 years, while in the eight without aortic involvement it was 8.4 years. Similar figures for the twenty-six cases of marked mitral stenosis and the six with only moderate mitral stenosis were 6.7 years and 10.1 years, respectively. It follows from the preceding analysis that aortic stenosis and mitral stenosis both tend to shorten, while tricuspid stenosis tends to lengthen, the duration of life after the onset of congestive failure.

Peripheral edema is common in all types of congestive heart failure and especially in cases of tricuspid stenosis. This is not invariably true,

for six of this series had no significant pitting edema. This may or may not have been the result of effective diuretic therapy. A subicteric tint of the skin is a frequent finding in tricuspid stenosis, but in this study it did not seem to be related to the severity of tricuspid stenosis. Cyanosis in tricuspid stenosis appeared to be more prominent than in other types of cardiac decompensation with the possible exception of chronic cor pulmonale. It also had a tendency to persist to some extent even when the patient had improved and was ambulatory. As pointed out by Altschule and Budnitz,[4] this cyanosis can be looked upon as a result of distention and engorgement of the peripheral veins and venules, and not as a result of a lowered oxygen content of the venous or arterial blood. Ascites occurred in slightly more than one-third of the cases and was distinctly more common in marked stenosis. In fact, ascites, requiring frequent abdominal paracentesis, is a conspicuous feature in some cases of tricuspid stenosis, resembling pericardial constriction in this respect. The presence of orthopnea proved difficult to appraise, for, as the condition progressed, it almost always developed. During the earlier stages, however, even when the liver was enlarged and ascites was present, orthopnea was often absent or negligible. Abdominal pain in the region of the liver was a frequent complaint, occurring in two-thirds of the cases, and was more marked in those with a higher degree of tricuspid stenosis. Although the liver was usually palpable (all but three cases), it appeared to be larger clinically than its actual post-mortem weight would indicate. In several instances definite liver expansile pulsations could be elicited.

Pulsation of the jugular veins is expected to be present in most cases of tricuspid disease. It will obviously be more prominent when there is a greater degree of tricuspid regurgitation and less stenosis. This proved to be the case, as it was much more frequent and more prominent in those with slight than in those with marked tricuspid stenosis. With these pulsations the veins were practically always found to be well distended. One characteristic feature of this distention was that it was apt to persist even when the patient had improved and had become ambulatory.[5] Determinations of venous pressure in the arm were made in only three instances. These readings were 300 mm., 340 mm., and 250 mm. of water. The changes in pressure were not followed with the cycles of improvement, but it is surmised that the pressure remains permanently elevated in all cases with appreciably stenosed tricuspid valves.

Auricular fibrillation was present in eighteen of the thirty-two cases. The average age at death for this group was 39 years and the average of the fourteen with regular rhythm was 29 years. This discrepancy cannot be explained on any difference in the degree of stenosis of the various valves, for there was more stenosis in the fibrillators than in the nonfibrillators. The average age at which the first rheumatic infection

occurred was identical in the two groups (i.e., fourteen years), and the duration of life from this first rheumatic infection was twenty-five years in the fibrillators and fifteen years in the nonfibrillators. A possible explanation of this discrepancy is that the proportion of patients who died of the complications of heart disease (rather than in pure failure) in the nonfibrillating group was greater than in the fibrillating group. If complications such as embolism and infection do not occur while the rhythm is regular, the patient may live on for many years, develop fibrillation, and then die of either heart failure or one of the complications.

There seemed to be a suggestive relationship between the relative size of the two auricles and the presence of auricular fibrillation. It is of interest that, of the seven cases in which the left and right auricle were judged to be of equal size, six had a regular rhythm and the other developed fibrillation not long before death. In the nineteen instances in which the right auricle was larger than the left, five were regular and fourteen were fibrillating. Three of the six cases in which the left auricle was larger than the right had a regular rhythm, and the other three had fibrillation. It would appear that an inequality in the size of the two auricles was an important factor in the development of auricular fibrillation.

The pulmonary second sound is accentuated in practically all cases of tricuspid stenosis, and this is to be accounted for by the invariable presence of mitral stenosis. One might surmise that the accentuation of P_2 would be greater when mitral stenosis is unaccompanied by tricuspid stenosis. An analysis of the murmurs that were present was extremely difficult because systolic and diastolic murmurs heard at the apex were frequently also detected to the left of the lower sternum, and it was impossible to distinguish whether the mitral or the tricuspid valve, or both, were the origin of such murmurs. In some cases it appeared that the murmurs near the sternum had a slightly louder or different character than those near the apex. On physical examination the heart size was always found to be enlarged. In general, both the right and left border of dullness extended beyond the normal limits. The average percussion measurements for the entire group were 5.4 cm. to the right and 13.7 cm. to the left of the midline. X-ray examination was carried out in ten of these cases and confirmed the clinical impressions. Measurements from heart plates showed the following average figures: right border 5.8 cm. to the right, left border 11.9 cm. to the left, and internal diameter of the chest 25.3 cm. This indicates that cases of tricuspid stenosis show considerable increase in the size of the heart in both directions, but particularly to the right. After the pathologic observations of these hearts one can definitely say that the increased size of the heart is due mainly to dilatation of the two auricles,

as the ventricles are not particularly dilated and only moderately hypertrophied.

Pulmonary congestion as evidenced by basal râles or hydrothorax was eventually present in all but two cases. In some cases it was strikingly slight or absent for some years when there was already peripheral edema and an enlarged liver. The degree of pulmonary congestion was distinctly greater in cases with marked tricuspid stenosis. Polycythemia was not an impressive finding, as the average red blood count was 4.8 million, and the average hemoglobin, 91 per cent. There was only one case with a red blood count of over six million. In general, those with more marked congestive failure had a higher count, and one can say that the group as a whole was characterized by a high normal red blood count.

The four electrocardiographic findings that were studied were the cardiac rhythm, the voltage of the QRS complex, the degree of axis deviation, and the form of the P wave. Electrocardiograms were available in twenty-seven of the thirty-two cases in this study. Of these, thirteen consistently showed auricular fibrillation in all tracings that were taken. Ten always showed a regular rhythm. There were two that were at first regular and later developed fibrillation. One other showed first auricular flutter and then developed fibrillation, and the last constantly had auricular flutter. The remaining five cases in which electrocardiograms were not taken had a regular rhythm. Auricular fibrillation or flutter was present in slightly less than half of the entire series.

The QRS complex was regarded as being of low voltage (5 mm. or less) in seven cases; all seven showed moderate to marked edema. In two cases electrocardiograms were obtained at different periods, and they showed that the height of the QRS complex increased as edema disappeared.

A study of the electrical axis revealed that in three cases there was no axis deviation. This may possibly be explained by the fact that there was a considerable degree of aortic stenosis. Only one had left axis deviation, and in this instance there was an associated hypertension. The remaining twenty-three all showed varying degrees of right axis deviation. Two of the latter developed right axis deviation during the course of a year of observation. No correlation could be discovered between the severity of stenosis of the various valves and the degree of right axis deviation.

The form of the auricular complex, or P wave, was studied in twelve cases. All showed some of the changes that are associated with auricular hypertrophy or dilatation. These changes consisted of broadening at the base, increase in height, a flat top, and notching of the P wave. The cases varied in the degree of change, but all showed one or more of these abnormalities. The peculiarities of the P wave were somewhat

more prominent in Lead I than in Lead II. The electrocardiographic findings discussed above are those commonly regarded as accompanying mitral stenosis. What part may be attributed to the tricuspid stenosis present in this group remains in doubt. It would appear, however, that in the presence of a regular rhythm the absence of right axis deviation and the abnormal P waves previously mentioned would cast doubt on the diagnosis of tricuspid stenosis.

Total proteins and the serum albumin-globulin ratio were determined in only five instances. The average total protein was 5.8 Gm. per cent; serum albumin, 3.2 Gm. per cent; and the serum globulin, 2.6 Gm. per cent. The degree of edema and ascites was apparently in direct proportion to the lowering of the serum albumin level in the few cases studied. Analysis of one of these cases was particularly significant because frequent determinations were made during the course of the disease. On admission there was massive general anasarca and the total protein was 4.3 Gm. per cent; serum albumin, 2.2 Gm. per cent and serum globulin, 2.1 Gm. per cent. In the following five weeks, during which time the patient was taking a very high protein diet and receiving diuretics, there was a gradual loss of about 50 pounds of water. The total protein was 6.0 Gm. per cent; albumin, 3.7 Gm. per cent; and globulin, 2.3 Gm. per cent. At this time she was essentially edema-free. Three years later, shortly before death, the readings were: total protein 4.5 Gm. per cent, serum albumin 1.9 Gm. per cent, and serum globulin 3.6 Gm. per cent. During these intervening three years she kept her weight low and remained edema-free on weekly injections of mercupurin. This case illustrates the importance of a low serum albumin level in the mechanism of edema and ascites in cases of tricuspid stenosis.

AGE AT DEATH OF PATIENTS WITH TRICUSPID STENOSIS

The average age at death in thirty-two cases of tricuspid stenosis was 34.3 years. The oldest was 51 years and the youngest was 17 years at the time of death. The average age for those with marked tricuspid stenosis was 32.5 years; with moderate tricuspid stenosis, 35.2 years; and with slight tricuspid stenosis, 35.8 years. Although the difference is slight, patients with a high degree of tricuspid stenosis seem to succumb at a younger age.

EFFECT OF CONCOMITANT MITRAL STENOSIS

An attempt was made to study the effect of the accompanying mitral stenosis (which was always present) on the age of death. The degree of stenosis of all valves was indicated by the terms slight, moderate, and marked. There were no instances in which the mitral valve was only slightly stenosed, and all cases showed as great as or a higher degree of mitral stenosis than of tricuspid stenosis. When stenosis was equal

in extent in the two valves, it was practically always of marked degree and the age at death was 32.5 years. When the degree of stenosis was somewhat greater in the mitral than in the tricuspid (the reverse was never true), the average age at death was distinctly greater (37.1 years) than when the valves were equally stenosed (32.5 years). Even among these cases with unequal stenosis in the two valves, those with slight degree of constriction lived longest with an average of 41.4 years for five cases with slight tricuspid stenosis and moderate mitral stenosis as compared to 35.0 years for ten cases with moderate tricuspid stenosis and severe mitral stenosis. On the other hand, when the discrepancy in the degree of stenosis was greater, i.e., slight tricuspid stenosis with a marked mitral stenosis, the average age in five cases was low (30.2 years). The fact that the patients with severe mitral stenosis associated with moderate tricuspid stenosis die at an older age than those with severe mitral stenosis and slight tricuspid stenosis indicates that it is the tricuspid valve that influences the duration of life in these cases.*

The obvious deduction that a greater degree of mechanical constriction of the mitral valve, apart from the condition of the tricuspid, indicates a graver condition is borne out by the finding that in twenty-six cases of marked mitral stenosis the average age at death was 33.0 years and in six cases of moderate mitral stenosis it was 40.8 years. One can conclude from the above analysis that, although mitral stenosis is the dominant lesion responsible for death, the time of death is determined by the accompanying tricuspid lesion and that, if the degree of stenosis of the latter is only slightly less than that of the former (i.e., moderate tricuspid stenosis and marked mitral stenosis), the maximum duration of life results.

Fatal cases with valvular disease can be arbitrarily divided into two groups, those dying with "pure" heart failure and those dying of complications. In the latter, death occurs from pulmonary infarction, peripheral emboli, intercurrent infections, subacute bacterial endocarditis, or any significant complication which terminates the natural progress of the disease prior to the final stage of fatal congestive failure. In the former, one may look upon the cardiac condition as having progressed to the advanced phase of irreversible congestive failure. When the thirty-two cases of tricuspid stenosis were divided into these two groups, we found that ten patients died with pure uncomplicated heart failure (all having marked mitral stenosis) at an average age of 31.2 years, while the other twenty-two patients in the second group died at an average age of 36.0 years. The reason for this paradoxical discrepancy is that the group with "pure failure" had a much higher degree of mitral and tricuspid stenosis and that the group dying of

*It will be shown later that a marked degree of aortic stenosis is associated with a still greater age at death, but analysis of this specific group of cases indicated that the effect of the tricuspid valve on the duration of life is independent of the aortic factor.

"complications" had the optimum ratio in the degree of stenosis between the two valves, i.e., the tricuspid valve having one degree less stenosis than the mitral valve. It is of interest that none of the patients with only slight tricuspid stenosis died of pure failure. The progress of their disease was not permitted to run its entire span, being interrupted by one or another complication which proved fatal.

EFFECT OF CONCOMITANT AORTIC STENOSIS

Among these thirty-two cases of tricuspid stenosis, all of which had mitral stenosis as well, there were twenty-four, or 75 per cent, that had definite aortic stenosis. Aortic stenosis was marked in eight, moderate in twelve, and slight in four. The average age at death of those with severe aortic stenosis was 40.0 years; for the moderate and slight aortic stenosis, 32.6 years; and for those without aortic stenosis, 32.7 years. A similar but even greater discrepancy was found when marked aortic stenosis was compared to moderate aortic stenosis, each group having similar degrees of stenosis of the mitral and tricuspid valves. It was found that all cases of marked aortic stenosis had an associated degree of mitral stenosis that was of equal severity. In fact it may be stated from this study that when there is some stenosis of the tricuspid valve, if the aortic valve can be identified as being markedly stenosed, one may be fairly certain that the mitral valve will be markedly stenosed and the tricuspid at least moderately stenosed. It is evident that a high degree of aortic stenosis accompanying mitral and tricuspid stenosis is either conducive to, or concomitant with, a longer life expectancy than if a lesser degree of aortic involvement is present.

PATHOLOGIC CONSIDERATIONS

The average heart weight of the entire group was 506 Gm. (twenty-eight cases). Those with marked tricuspid stenosis had slightly heavier hearts. This figure seems much smaller than one might have expected from the large size of the heart and the great frequency of aortic stenosis. The explanation is that the large cardiac silhouette is due mainly to dilatation of the auricles, and the aortic stenosis does not continue for a great many years as it does in the pure aortic stenosis of older people, when it produces extreme hypertrophy of the left ventricle.

Estimates were made of the relative degree of enlargement of the right and left auricles from the description given in the autopsy protocols. All cases apparently had some enlargement of both auricles. The relative enlargement of the right auricle as compared to the left was decidedly greater in those with marked tricuspid stenosis than in those with lesser degrees of stenosis. The average thickness of the right ventricle was 5.5 mm. for the entire group, 6.1 mm. for those with marked tricuspid stenosis, and 5.1 for the remainder (normal about 4.0

mm.). When the group having slight tricuspid stenosis and marked mitral stenosis is compared with one having marked tricuspid stenosis and marked mitral stenosis, the average thickness of the former was found to be 7.0 mm. (five cases) and, of the latter, 6.1 mm. (nine cases). The inference follows that, whereas right ventricular hypertrophy results from mitral stenosis, an accompanying tricuspid stenosis tends to diminish the degree of right ventricular hypertrophy. Measurements of the left ventricle showed average figures of 16.0 mm. for the entire group, 18.0 mm. for those with marked tricuspid stenosis, and 14.7 mm. for the less stenosed cases (normal about 14.0 mm.). The greater thickness of the left ventricle in the cases of marked tricuspid stenosis was not due to the effect of the tricuspid valve, but to the greater incidence of marked aortic stenosis present in these cases. This is borne out by the figures for the relative thickness of the left ventricle in marked, moderate, and slight aortic stenosis which were 20.5 mm., 16.7 mm. and 16.0 mm., respectively. It was to be expected that the higher degrees of aortic stenosis would be accompanied by a thicker left ventricle.

The condition of the coronary arteries was investigated, and in only two was any significant degree of coronary sclerosis detected. Pericardial adhesions of greater or lesser extent were found in 42 per cent of the cases. This is a common finding in all types of rheumatic heart disease. Slight degrees of hydropericardium (less than 200 c.c.) were found in about a third of the cases, although in one case 1,000 c.c. of pericardial fluid were present.

Pulmonary infarctions were common, occurring in about half the cases. In general, peripheral arterial emboli occurred with about the same frequency as pulmonary infarction. The average weight of the liver showed interesting variations with different degrees of tricuspid stenosis. Whereas the average for the entire group was 1,535 Gm., the figures for marked, moderate, and slight tricuspid stenosis were 1,497, 1,393, and 1,755 Gm., respectively. Those with slight stenosis had the largest livers, probably because there were more congestion and less fibrosis in the liver.

Analysis was made of the accuracy of the clinical diagnosis of the various valve lesions. Mitral stenosis was recognized antemortem in every one of the thirty-two cases. Most of these also had an apical systolic murmur which could be considered indicative of concomitant mitral insufficiency. Of the twenty-four cases of aortic stenosis, thirteen were diagnosed definitely antemortem, and one was considered as having questionable aortic stenosis. In the other ten the presence of aortic stenosis was not recognized clinically. Moreover, it was thought to be present in four cases of the eight that did not have aortic stenosis. In other words, the accuracy of the diagnosis of presence or absence of aortic stenosis was slightly better than 50 per cent. A diastolic murmur

was heard either in the aortic area or along the upper left sternal border, which was interpreted as being due to an aortic insufficiency in sixteen of the thirty-two cases. Three of these were instances in which the presence of aortic stenosis was overlooked, but the finding of an aortic diastolic murmur at least enabled the clinician to incriminate the aortic valve as being involved. It is of interest that whenever aortic diastolic murmurs were heard (with two exceptions) there was pathologic evidence of aortic stenosis. The inference is that in cases with tricuspid stenosis, if one can diagnose aortic insufficiency, it is fairly safe to assume that aortic stenosis is present.

As was stated in the beginning of this paper, tricuspid stenosis has been, and still is, the most difficult of all common valvular lesions to diagnose. Only five of these thirty-two cases were regarded as having definite tricuspid stenosis antemortem, and one additional case as having questionable tricuspid stenosis. Even these figures do not tell quite the whole story, as different observers disagreed frequently in their diagnoses. Contrariwise, some of the cases that were overlooked would probably have been recognized if they had been examined by those especially trained in cardiovascular disease. During the past few years, because of increased interest in the recognition of tricuspid stenosis, greater diagnostic accuracy has been attained. This is shown by the fact that two of the last four cases of tricuspid stenosis were correctly diagnosed antemortem.*

DISCUSSION

A study of tricuspid stenosis really consists of an analysis of trivalvular stenosis, for it is clear from this review that all cases of tricuspid stenosis have an accompanying mitral stenosis and in most (75 per cent) aortic stenosis is also present. In fact, the degree of mitral stenosis is generally quite marked. It would therefore be impossible to distinguish the effects of one valve without considering those of the other valves.

Tricuspid endocarditis is still regarded as rare despite the fact that Dressler and Fischer[6] found that it was present in 24 per cent of all cases of rheumatic endocardial involvement. This closely corresponds to the figure obtained in this study (27 per cent). Several reports of individual or small groups of cases have been reported by various

*It was the following experience (not included in this series) that crystallized in our minds some of the views concerning tricuspid stenosis and prompted this present study. A woman, aged 48, was seen in consultation with Dr. Phillip Marvel of Atlantic City in 1930. Some twelve or thirteen years before she had been examined by an outstanding consultant when she showed evidence of congestive failure, and the prognosis was estimated as a few weeks. She had such marked edema at that time that Southey tubes were used. Despite this bad prognosis, she carried on in moderate comfort for about fourteen years and even for two years after being seen by one of us. She showed obvious signs of mitral stenosis, auricular fibrillation, enlarged liver, ascites, and peripheral edema. Most of these signs had been present to a varying degree all these years. Because she had so much right-sided failure out of proportion to the degree of dyspnea for such a long time, a diagnosis of tricuspid stenosis was made. Post-mortem examination by her own physicians revealed stenosis of tricuspid, mitral, and aortic valves.

authors.[7-15] Although there was no instance of pure tricuspid stenosis in this series, such a case was reported by Clemens.[16]

The study of the age at death in different cases of tricuspid stenosis proved to be of some interest. Although the number of cases was small, the effects of the degree of tricuspid stenosis and of the additional valvular lesions were studied. Clinicians have long suspected that the presence of one valvular defect influences the course of events in the presence of another valvular defect. Likewise it has been thought that hypertension has a favorable effect on the progress of mitral stenosis.[2] It appeared from this study that with the same degree of mitral stenosis the presence of tricuspid stenosis and/or aortic stenosis tended to lengthen the duration of life. It was predicted that, when marked mitral stenosis is present, a moderate degree of tricuspid stenosis and a marked degree of aortic stenosis would result in the greatest longevity. Although only three cases in the entire series corresponded to these criteria, it is of interest that the average age at death of these three was 46 years, compared to the general average of all thirty-two cases of 34.3 years.

In the analysis of the clinical course of these cases, the duration of symptoms, and the age at death it appeared that the optimum pattern for a given degree of mitral stenosis was a slightly lesser degree of tricuspid stenosis, i.e., moderate tricuspid stenosis with marked mitral stenosis and slight tricuspid stenosis with moderate mitral stenosis. It was also evident that, from every angle investigated, those patients with moderate tricuspid stenosis did better than those with either slight or marked tricuspid stenosis. This latter observation might be looked upon as a corollary of the former statement inasmuch as most of the patients had marked mitral stenosis. An indication of the beneficial effect of aortic stenosis was observed when patients dying before the age of 30 years (twelve cases) were compared with those dying after the age of 40 years (nine cases). The former had distinctly less aortic stenosis than the latter.

One may speculate as to the significance of these curious relationships. In the development of the disabling complications of heart failure, peripheral edema and engorged liver (right-sided failure) are much less vital than pulmonary congestion (left-sided failure). There is comparatively little harm that results from even considerable edema of the legs. Even hepatic congestion may be present for many years and be compatible with an ambulatory existence. In the course of time this may result in depression in the liver function with hypoproteinemia or in cirrhosis of the liver with portal obstruction, but apart from abdominal pain and some other minor symptoms it does not play a dominant role in the causation of death. The main hazards with which most cardiac patients are faced are related to the lungs. Pulmonary

infection, infarction, and congestion with the resultant suffocation and lack of adequate oxygen exchange are the main causes of disability and mortality. With the development of mitral stenosis the concomitant presence of some degree of tricuspid stenosis serves to protect the pulmonary circuit by diminishing the return flow of blood to the lungs. With a normal tricuspid valve the vigorous contraction of an hypertrophied right ventricle keeps propelling blood into the pulmonary vessels too rapidly and in too great quantity to flow through a markedly narrowed mitral orifice. The result is stagnation in the lung, pulmonary congestion, and breathlessness. The diminished return to the right ventricle as a result of tricuspid stenosis partly offsets this imbalance. In a different manner aortic valvular involvement (or hypertension) may have a beneficial effect. They both would tend to enlarge and dilate the left ventricular cavity and stretch the mitral ring, thereby retarding the progressive constriction of the mitral stenosis. Furthermore, inasmuch as congestive failure is essentially the result of an imbalance between the two ventricles, hypertension and aortic valvular disease produce a burden on the left ventricle, and mitral stenosis, on the right ventricle; a better balance is thereby maintained. These physiologic and dynamic relationships help to explain the clinical observations relating to the effect one lesion has upon the other.

From a theoretical point of view, the left ventricle should be small in pure mitral stenosis and the right ventricle should be small in pure tricuspid stenosis because of the diminished work of the respective chambers. On the other hand aortic stenosis should cause left ventricular and mitral stenosis right ventricular hypertrophy. Because all cases in this study had combined lesions these relationships could be studied only by comparing those with different degrees of stenosis of various valves. In this way it appeared that tricuspid stenosis did tend to diminish the degree of right ventricular hypertrophy which was resulting from the accompanying mitral stenosis. This serves as further evidence of the protective action of tricuspid stenosis on mitral stenosis. Likewise it would be expected that all of these cases would show both left and right auricular enlargement, the former from the mitral stenosis and the latter from the tricuspid stenosis. This not only proved to be the case, but those with a higher degree of tricuspid stenosis had a greater degree of hypertrophy and dilatation of the right auricle. Accurate measurements of the capacity of the auricles were not made, but the fact that the right auricle can be enormous in tricuspid stenosis is illustrated by the case reported by Taussig[14] in which it was found to contain 2,150 c.c. while the capacity of the left auricle was only 95 to 100 c.c.

A very high incidence of pericardial adhesions was found among these cases (42 per cent). We interpret this as indicating that acute pericarditis is frequent in the early attacks of rheumatic infection in patients

who develop tricuspid stenosis. None of them, however, seemed to have the constricting type of pericarditis, although many of the extracardiac features of tricuspid stenosis closely resemble those seen in classical constrictive pericarditis. The fact that adhesions were less pronounced in those with marked than in those with lesser degrees of tricuspid stenosis would also tend to support the view that they had no relationship to the high degree of peripheral venous congestion.

The average weight of the liver was not as great (1,535 Gm.) as was expected, considering that the liver was practically always felt a considerable distance below the right costal margin. Possibly because of the loss of body tissue and muscular tone that is so common in chronic cardiac disease, there is a certain degree of ptosis as well as enlargement of the liver. It is of interest that the weight of the liver was greater in cases of slight tricuspid stenosis than with more marked tricuspid stenosis. This may indicate that with prolonged stasis the amount of fibrous tissue may increase while the amount of blood decreases.

Ascites although a prominent feature in some cases was by no means always present. In a few cases in which determinations were made the blood proteins (mainly the albumin) were diminished. This probably was related to the damaged liver function and, when present, must be an important factor in the production of edema and ascites. Increased venous pressure obviously is a further factor in the production of edema. This was always found elevated in tricuspid stenosis, and, as has been shown by Altschule and Budnitz,[4] remains elevated even when compensation is fairly well established and the patients are ambulatory. However, some cases of tricuspid stenosis may show no peripheral pitting. A third factor is the massaging effect of muscular activity that helps in the return flow of fluid from the legs. We believe that, when there is no hypoproteinemia and lack of dyspnea enables the patient to remain ambulatory (rather than inactive), the muscular activity of the legs helps to delay or prevent edema despite the high venous pressure.

As a result of the prolonged hepatic congestion many patients with tricuspid stenosis develop a peculiar icteric tint known to the older clinicians and discussed by Wearn.[12] It may be described as an olive discoloration of the skin which consists of a combination of slight icterus and slight cyanosis.

In our analysis of the relation between the time and number of attacks of rheumatic fever and the ultimate degree of valvular damage and age at death, certain significant observations were made. In the entire group there was a higher incidence of previous rheumatic fever or chorea (78 per cent) than is customarily obtained in routine hospital cases of rheumatic valvular disease. Despite this it appeared that the number of repeated rheumatic infections bore no relationship to the

severity of the cardiac damage, for cases with slight tricuspid stenosis had more frequent rheumatic bouts than those with more marked tricuspid stenosis. This would seem to indicate that the degree of endocardial damage is more closely related to the peculiar reactions of the host to the initial infection than to the frequency of repeated attacks. This somewhat presupposes that cardiac involvement began in all cases with the first infection which cannot be ascertained from our data. However, the average interval between the first rheumatic infection and death was about the same (20.6 years) for the various degrees of tricuspid stenosis. All this makes one suspect that the response of the individual host is an important factor in the development of rheumatic heart disease.

The clinical picture of tricuspid stenosis was well described by Shattuck, quoted by Futcher,[9] i.e., "whether a presystolic souffle can be heard or not, tricuspid stenosis can be pretty safely diagnosticated if the patient is a female with a rheumatic history, has mitral stenosis, perhaps also aortic disease and presents the evidence of prolonged or recurrent venous stasis of greater or lesser degree." In some cases abdominal pain due to the enlarged liver is a prominent feature. When the systolic pulsations are marked in the distended veins, one infers that the major defect is insufficiency of the tricuspid valve and, when they are absent, it is more likely that a high degree of stenosis is present. Venous distension is most significant if present in the upright position and while the patient is in a fair state of compensation. Pulsations of veins are often observed in the temporal vessels where they will not be confused with neighboring arterial pulsations. As was pointed out by Herrick,[8] patients may appear to be remarkably comfortable even though there are considerable edema, ascites, and cyanosis. Features suggestive of pericardial disease, simulating constrictive pericarditis, may be present, such as systolic retraction of the apex, Broadbent's sign, and failure of the heart to shift with change of bodily position. Considerable cardiac enlargement, the presence of valvular disease, and the marked precordial activity, however, practically rule out constrictive pericarditis.

The findings in the heart are mainly those seen in mitral stenosis. There will be marked cardiac enlargement, especially to the right. The pulmonary second sound will be increased in intensity but not, as a rule, to the same extent as in uncomplicated mitral stenosis. A regular rhythm will be found as frequently as auricular fibrillation, with an occasional case developing auricular flutter. It would seem that auricular fibrillation is not as common in tricuspid stenosis when marked congestive failure is present as is the case with mitral stenosis alone. The murmurs of mitral involvement will be heard at the apex (diastolic or presystolic and probably a systolic murmur). If these murmurs become louder or change their character toward the xiphoid region, one may suspect that

they have their origin in the tricuspid valve. Along the upper left sternal border and in the aortic area many cases will show a fairly loud systolic murmur and possibly a systolic thrill and even a blowing diastolic murmur. These latter signs indicate an accompanying aortic stenosis.

The findings in the chest will vary considerably. Some will have very little if any evidence of congestion and others will show few or many moist basal râles or the signs of hydrothorax. One is often struck with the paucity of pulmonary signs in the presence of marked peripheral and hepatic congestion. The liver is generally enlarged, palpable and pulsating, but absence of a palpable liver does not rule out tricuspid stenosis. On rare occasions the venous auricular "a" wave may be detected in tracings taken over the liver.[6, 15, 17] Hypertension is almost invariably absent and may be helpful in distinguishing patients with mitral stenosis and hypertension who do well for many years from those with mitral and tricuspid stenosis who similarly carry on for a surprisingly long time.

Laboratory findings are likely to show a high normal or slightly increased icteric index. Polycythemia may be present but is exceptional. One is more likely to find a high normal red cell count and hemoglobin level. Venous pressure will invariably be elevated. Excursions in the manometer will vary from 0.4 to 2.0 cm. of water with various phases of the cardiac cycle. The greater variations indicate a predominant element of tricuspid insufficiency rather than tricuspid stenosis.[4] The velocity of blood flow will be slightly slowed even in the presence of compensation and will be markedly slowed with congestive failure.[4] The serum proteins may be low and to some degree will determine the presence or absence of edema and ascites.

Roentgenologic examination may reveal calcification of the mitral or aortic valve, but the tricuspid valve has not as yet been identified in this fashion. Dilatation of the left auricle can easily be visualized, but the same is not true of the right auricle. Pulmonary congestion may be very slight considering the degree of heart failure. Electrocardiography may also be of some help. If right axis deviation is not present and some nonvalvular cause for left ventricular hypertrophy such as hypertension is absent, one should hesitate in diagnosing tricuspid stenosis. Practically all cases will show right axis deviation, and the few in which there is no axis deviation will have aortic stenosis. Ventricular complexes of low amplitude are common but generally are related to the presence of considerable edema. Such complexes tend to return to a normal voltage with the disappearance of edema. When the heart rhythm is regular, peculiar "P" waves indicating dilatation and hypertrophy of the auricles will almost invariably be noted.

A study of the comparative degree of stenosis of the three valves revealed certain interesting relationships. When the diagnosis of

tricuspid stenosis can be made and evidence of well-marked aortic stenosis can also be identified, one can be sure that the mitral valve will be markedly stenosed and the tricuspid at least moderately so. If the tricuspid valve is markedly stenosed, there will always be marked mitral stenosis.

The most significant aspect of this group of cases or the reason that more accurate diagnosis of tricuspid stenosis is of some importance is that one can give a much more hopeful prognosis after the onset of congestive failure than in any other type of chronic valvular disease. The average duration of life after the initial symptoms of congestion was 7.5 years. As has been reported before,[13] this is about twice as long as for other types of valvular disease.

SUMMARY AND CONCLUSIONS

1. In a study of 4,437 autopsies performed at the Peter Bent Brigham Hospital from 1913 to 1940 inclusive, there were 340 cases of chronic rheumatic valvular disease, of which thirty-two had tricuspid stenosis. These latter were equally divided into three groups, i.e., slight, moderate, and marked. There were an additional sixty cases of organic tricuspid involvement without a significant degree of stenosis.

2. The incidence of chronic rheumatic valvular disease in general and tricuspid stenosis in particular was 7.7 and 0.7 per cent, respectively, of all cases examined post-mortem. Tricuspid stenosis was found in 9.4 per cent of cases of chronic rheumatic valvular disease and in 14 per cent of cases of mitral stenosis. If those showing tricuspid involvement without stenosis are included, these figures are 27 per cent and 41 per cent, respectively.

3. Mitral stenosis (almost invariably marked) was found in 100 per cent and aortic stenosis in 75 per cent of the thirty-two cases of tricuspid stenosis. The degree of tricuspid stenosis was never greater than that of the mitral valve.

4. The average age at death was 34.3 years, which is considerably less than for other chronic valvular disease although the duration of heart failure was decidedly greater. Those with marked tricuspid stenosis died at a younger age than those with lesser degrees of stenosis.

5. Concomitant tricuspid stenosis and/or aortic stenosis was shown to have an effect on the progress of mitral stenosis. Aortic stenosis tended to shorten and tricuspid stenosis to lengthen the duration of failure although both added to longevity.

6. It was found that the clinical course largely depended on the correlation of stenosis of the three valves and that the optimum pattern for those having marked mitral stenosis was moderate tricuspid and marked aortic stenosis.

7. Pathologic studies showed that the average weight of the heart was 506 Gm. and that of the liver was 1,535 Gm. These figures seem smaller

than expected and their significance was discussed. Both auricles were almost always conspicuously dilated, especially the right. The degree of hypertrophy of the right ventricle was only moderate considering the marked mitral stenosis present. Chronic nonconstrictive pericarditis was found in half of the cases.

8. A past history of rheumatic infection was present in 78 per cent of the cases, but the frequency of rheumatic bouts had no relation to the degree of valvular stenosis or to the duration of life. It seemed that the peculiar reaction of the individual host was an important factor in determining the ultimate results.

9. The clinical picture seemed to depend upon the relative degree of stenosis of the aortic, mitral, and tricuspid valves. Practically all cases showed evidence of increased venous pressure, enlarged liver, marked cardiac enlargement (especially to the right), and a peculiar discoloration of the skin, consisting of a subicteric and slightly cyanotic tint. The extent of pulmonary congestion varied, and there was a notable absence of hypertension. The degree of edema and ascites was influenced by a lowering of the serum proteins. It is believed that tricuspid stenosis tends to delay the development of dyspnea and orthopnea that otherwise might occur in severe mitral stenosis by impeding the return flow of blood to the lungs.

10. Auricular fibrillation was present in about half of the cases despite the high degree of mitral stenosis, and those with regular rhythm died at an earlier age. Electrocardiograms almost always showed right axis deviation, and in those with regular rhythm the P waves were always of an abnormal form.

11. Mitral stenosis was diagnosed antemortem in all cases; aortic stenosis, in 50 per cent; and tricuspid in only five instances. The means for improving the accuracy of diagnosis of tricuspid stenosis and trivalvular stenosis have been discussed.

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MECHANISMS INVOLVED IN ACUTE FATAL NONTRAUMATIC COLLAPSE ASSOCIATED WITH PHYSICAL EXERTION

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THE problem of acute, fatal, nontraumatic collapse during sport and work has recently been investigated by Jokl and Melzer (1940) and by Cluver and Jokl (1941). An analysis of sixty-six cases, in which clinical data as well as complete autopsy reports were available, revealed that collapse associated with exertion is almost invariably due to circulatory disease of long standing. In no case in which death occurred in connection with physical exertion was the subject found at autopsy to be free of serious disease.

PATHOLOGIC FINDINGS

The following conditions, arranged in order of frequency, were found at autopsy:

1. Coronary artery disease.
2. Acute coronary occlusion.
3. Degenerative disease of heart muscle.
4. Ruptured aneurysm of aorta.
5. Chronic inflammatory disease of heart muscle.
6. Ruptured aneurysm of cerebral arteries, usually congenital.
7. Rupture of heart.
8. Rupture of congenitally diseased aorta.
9. Developmental abnormalities of the heart.
10. Developmental hypoplasia of entire arterial system.

Thus, of the three "master systems of the body" (Spilsbury, 1937), the circulatory, the respiratory, and the nervous, the circulatory is by far the most frequently involved in fatal nontraumatic collapse associated with work and sport.‡

PATHOPHYSIOLOGIC CONSIDERATIONS

For the analysis of the functional mechanisms involved in the breakdown of the diseased circulatory system during exertion, the following physiologic reactions must be considered:

1. *The Biphasic Reaction of the Arterial Blood Pressure to Exercise.*—Physiologically arterial blood pressure rises during exercise and drops

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‡A tabulated account of the findings in each case is given in the S. Afr. J. M. Sc. 5: 4, 1940. A further report will appear in the AM. HEART J. (in press).

below the initial level during the rest period following exertion. We therefore speak of the "biphasic reaction to exercise." Whenever the autopsy revealed that death had been due to rupture of diseased blood vessels, it was ascertained that the first symptoms of the collapse which preceded death had set in *during* the muscular effort. As muscular exertion is accompanied by a rise of arterial systolic blood pressure, this physiologic reaction is therefore considered directly responsible for the rupturing of the affected blood vessels.

The phase of elevated blood pressure during exercise is followed by a depression during the rest period *after* the exertion, when the arterial pressure usually drops lower than the initial level. During this "negative phase," the significance of which for the coronary blood supply has recently been stressed by Blumgart, Schlesinger, and Davis (1940), there is distinct danger to subjects who suffer from coronary and myocardial disease.

Among our own cases was that of a football player who lost consciousness *after* a league match and died thirty minutes later. At autopsy his heart muscle showed general hypertrophy and advanced fibrosis. Another example is that of a 16-year-old girl who, having collapsed after dancing almost uninterruptedly for three hours, died a few minutes later. At autopsy, examination revealed congenital subaortic stenosis, marked hypertrophy of the left ventricle, and advanced myocardial degeneration.

2. *Expiratory Effort ("Valsalva" Phenomenon.)*—We consider that expiratory effort with the closed glottis represents the greatest physiologic stress with which the heart has to cope.

The diffusion of oxygen through the lung is virtually suspended, and oxygen saturation of the capillary blood consequently decreases rapidly. This decrease has been shown by Matthes (1935) to be most marked during or immediately after exercise when the oxygen requirements of the tissues are raised. Moreover, the elevated intrathoracic pressure impedes the return of blood to the right auricle, leading to a sharp increase of systemic venous pressure (Baumann, 1935). The diminished output of the right ventricle as well as the greatly increased intrapulmonary pressure seriously interferes with the pulmonary circulation, leading to deficient filling of the left ventricle which through the fluoroscope can be seen to "beat empty" ("leerschlagen"). Thus, the filling of, and the pressure in, the ascending aorta decrease acutely, and the coronary blood flow consequently diminishes sharply. Visscher (1939) has drawn attention to what he calls "the pressure gradient mechanism" on which the coronary blood flow, like any other fluid in an hydraulic system, depends. "This pressure gradient," he says, "so far as the coronary system is concerned, is measured by the difference in pressure between aorta, and the coronary sinus and right

ventricle." As the intra-aortic pressure decreases during expiratory effort, the pressure gradient flattens and the coronary blood supply decreases sharply. Thus, myocardial respiration is greatly impaired. Although reflexes from the carotid sinus and aortic arch, in the face of a lowered aortic pressure, usually lead to a rise of *peripheral* arterial pressure due to arteriolar vasoconstriction (Bürger, 1935; Heymans, 1937), myocardial blood supply is likely to suffer greatly.

The profound pathophysiologic significance of this phase must be viewed in the light of the classic work of Shipley, Shipley, and Wearn (1935). These authors showed that a pathologically hypertrophied heart muscle possesses, per unit of myocardial tissue, a considerably smaller number of capillaries than a normal heart muscle. The area of myocardial tissue supplied by a single capillary, is enlarged in the pathologically hypertrophied heart. It exceeds greatly the equivalent area in the heart of the healthy, though untrained, subject. The richest capillary supply is found in the heart of the trained healthy athlete (Petren, Sjöstrand and Sylven, 1936). This is the reason why the heart of *trained healthy* subjects, whose respiratory tissue requirements are readily satisfied, will practically never be endangered, even in the course of strenuous athletic performances which demand extreme expiratory efforts, whereas, on the other hand, impeded myocardial blood supply implies a considerable risk in *all* situations, in which expiratory effort against the closed glottis occurs. Exercise represents one of these situations.

In subjects with coronary artery disease, and deficient capillary supply of a hypertrophic myocardium, this physiologic phase therefore often represents a catastrophic event from which the heart may never recover. Sudden death has frequently been encountered in middle aged and, occasionally, in young persons, in the course of physical activities, such as carrying heavy weights, gymnastic exercises, pushing a wheel-barrow, cycling up hill, or wrestling. In the majority of these cases autopsy revealed coronary and myocardial disease.

3. *The Gastrocoronary Reflex.*—Rise of intragastric pressure, especially, it is claimed, in the proximal portion of the stomach, elicits a reflex constriction of the coronary arterial system. The practical importance of the gastrocoronary reflex was first stressed by G. von Bergmann (1936) at whose clinic it had been investigated (Dietrich and Schwiegk, 1933, 1934). Subsequently, the physiologic and clinical implications of this problem were carefully studied by N. C. Gilbert and collaborators (1939, 1940) and others. During physical exertion, when the oxygen requirements of the myocardium are considerably increased, the gastrocoronary reflex may result in serious anoxemia in the heart in which the tissue respiration is already impaired by disease. It has been shown by Jarisch and Liljestrand (1927), that even the healthy circulation functions less economically if the stomach is dis-

tended, a result which represents the scientific basis for the empirical rule that after meals strenuous exercise is inadvisable. We therefore attach significance to the fact that in seven of our own cases the stomach was found distended with food. Two subjects were known to have taken part in strenuous games immediately after having consumed big meals. When they collapsed, they vomited very large quantities of undigested food, whereafter they experienced temporary symptomatic relief. Spilsbury (1937) reported the case of a young woman who collapsed while skipping after a meal and died shortly afterward. Autopsy revealed congenital absence of the left branch of the coronary artery. It may be assumed that in this instance the gastrocoronary reflex had caused a critical reduction of the oxygen supply to the myocardium.

PHYSICAL EFFICIENCY AND CIRCULATORY DISEASE

It is remarkable that cardiovascular disease, so serious that it may cause death at any moment, does not necessarily interfere with even an extraordinarily high standard of physical efficiency. Jokl and Parade (1933) described several cases of athletes with valvular defects. Jokl and Suzman (1940) have studied a marathon champion with aortic regurgitation and mitral stenosis. Suzman* has recently observed a young wrestler who, in spite of the presence of mitral stenosis with enormous dilation of the heart and signs of congestive cardiac failure with cyanosis, continued, against advice, to take part successfully in wrestling bouts. Cluver and Jokl (1941) have communicated the case of "The Iron Man of South African Rugby," who died a few minutes after a test game in which he excelled in the same way as on innumerable previous occasions. Autopsy revealed a grossly underdeveloped abdominal aorta, an almost totally degenerated left, and a grossly hypertrophied right, kidney, a hypertrophied and degenerated heart muscle, an underdeveloped, partly obliterated, atheromatous coronary artery, and a large thymus gland, which, from the histologic appearance, could be assumed to have been functionally active. This collection of pathologic features must have been present for many years, and yet the "patient" had been one of the most outstanding rugby players in the world during the decade preceding his death. An identical twin brother of the deceased had died a short time before, also during physical exertion (swimming)!

We have included in this analysis only *nontraumatic* collapses. No reference is made to the large number of athletic fatalities of traumatic origin, most of which are due to injury to the central nervous system. As an example of this group, Jokl (1941) has recently analyzed a branch of sport (boxing) in which specific athletic traumata are frequently primarily responsible for fatal incidents. With regard to *nontraumatic*

*Unpublished data.

fatal collapses during or after effort, the position is entirely different. A person who dies during exertion would, in most cases, otherwise have become the victim of some other physiologic activity. While normally no conceivable functional strain can cause fatal collapse (Suzman and Jokl, 1936), certain diseases, such as those enumerated in this paper, render heart and blood vessels so vulnerable that the physiologic effort associated with physical exertion may overtax their adaptive plasticity.

SUMMARY

The results of an analysis of sixty-six cases of sudden death from physical exertion are discussed. The pathologic findings are given and interpreted.

A special attempt has been made to clarify the part played by physiologic reactions to exercises, in leading to the fatal breakdown. The following physiologic phenomena have been considered in detail: (1) The biphasic reaction of the arterial blood pressure to exercise, (2) expiratory effort (Valsalva phenomenon), and (3) the gastrocoronary reflex.

Attention has been drawn to the fact that even advanced circulatory disease is not necessarily accompanied by a decrease or a low state of physical efficiency.

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THE COLD-PRESSOR TEST IN SUBJECTS WITH NORMAL BLOOD PRESSURE

Report of Observations on 350 Subjects, With Special Reference to the Family History

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ACCORDING to Hines,[1] "vascular hyperreactivity," as measured by the cold-pressor test, indicates "a prehypertensive phase of the syndrome which is designated as essential hypertension." He bases his conclusions on the observations that (1) hyperreaction to the cold-pressor test among people with normal blood pressure is similar to the reaction observed in essential hypertension; (2) patients who were formerly hypertensive show a hyperreactive response even though their blood pressure is normal; (3) the incidence of hyperreaction in children equals the combined incidence of hyperreaction and hypertension among adults; (4) subjects with normal blood pressure who show a hyperreaction generally come from families in which there is a high incidence of hypertensive cardiovascular disease; and (5) hypertension has developed in a few patients whose blood pressure was once normal, but who showed hyperreaction to the test.

We are presenting this series of observations on 350 people with normal blood pressure because our results with regard to the family history do not agree with those of Hines. As far as we know, there have been only two reports of cold-pressor studies, made with Hines' exact technique, which have included a larger number of subjects with normal blood pressure. In 1940, Hines[1] published the results of cold-pressor tests on 1,015 people with usually normal blood pressure, and Chesley and Chesley[2] have analyzed cold-pressor tests on 539 pregnant women.

TECHNIQUE OF COLD-PRESSOR TESTS

The procedure as outlined by Hines was followed throughout. The subject reclined in a quiet room for a period of twenty to sixty minutes. Blood pressure measurements were made at intervals until a basal level was reached. The cuff of the sphygmomanometer was left on one arm, and, after the basal level was attained, the opposite hand was plunged into water at a temperature of 3 to 5° C. (37.4 to 41° F.). The hand was kept immersed to a level just above the wrist for sixty seconds. The blood pressure was measured at thirty and sixty seconds.

The difference between the basal level and the maximum reading is said to be the response. Using Hines' criteria, subjects whose response exceeded 20 mm., systolic, and 15 mm., diastolic, were called hyperreactors. Those whose response did not exceed these figures were designated as hyporeactors.

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SUBJECTS OF TESTS, AND RESPONSE

The test was performed on 350 office workers with normal blood pressure. In so far as response to the cold-pressor test is concerned, they were selected at random. The blood pressure was arbitrarily said to be normal if it fell below 145 mm., systolic, and 95 mm., diastolic, after twenty minutes or more of rest in the reclining position. There were 260 men and ninety women. The average age was 37 years, and the range of age was 21 to 67. The results are summarized in Table I. The average response to the cold-pressor test was 16.09 ± 0.34* mm., systolic, and 15.67 ± 0.30 mm., diastolic. The range of response was –4 mm. to 56 mm., systolic, and 0 mm. to 45 mm., diastolic. There were only two subjects with a negative systolic response and none with a negative diastolic response. There were 104 hyperreactors (eighty males and twenty-four females), and the average response was 27.68 ± 0.45 mm., systolic, and 24.37 ± 0.45 mm., diastolic. Among the 246 hyporeactors (180 males and sixty-six females), the average response was 11.35 ± 0.21 mm., systolic, and 11.99 ± 0.25 mm., diastolic.

TABLE I

SUMMARY OF RESULTS WITH THE COLD-PRESSOR TEST

SUBJECTS				MEAN RISE OF BLOOD PRESSURE IN MILLIMETERS OF MERCURY	
	NUMBER	MALES	FEMALES	SYSTOLIC	DIASTOLIC
Entire group	350	260	90	16.09±0.34	15.67±0.30
Hyperreactors	104	80	24	27.68±0.45	24.37±0.45
Hyporeactors	246	180	66	11.35±0.21	11.99±0.25

TABLE II

AGE AND HYPERREACTION TO THE COLD-PRESSOR TEST

SUBJECTS		HYPERREACTORS	
	NUMBER	NUMBER	PERCENTAGE
Entire group	350	104	29.7
Ages 20-29	52	18	34.6
Ages 30-39	205	54	26.3
Ages 40-49	53	14	26.4
Ages 50 and over	40	18	45.0

Table II shows the effect of age on the response to the cold-pressor test. In the entire group, 104 (29.7 per cent) were hyperreactors. There were fifty-two subjects between the ages of 20 and 29, and, among these, eighteen (34.6 per cent) were hyperreactors. Among 205 persons between the ages of 30 and 39, there were fifty-four (26.3 per cent) who were hyperreactors. Between the ages of 40 and 49, there were fourteen (26.4 per cent) hyperreactors among fifty-three subjects. There were forty persons past the age of 50, and eighteen (45 per cent) showed hyperreaction to the cold-pressor test.

*The figure after the sign is the probable error of the arithmetic mean.

THE FAMILY HISTORY

Table III shows that the response to the cold-pressor test was not related to the family history in the present series. One or more instances of hypertensive cardiovascular disease were found in the family histories of ninety-six (27.4 per cent) of the entire group when parents and siblings were counted. Thirty-one (29.8 per cent) hyperreactors and sixty-five (26.4 per cent) hyporeactors had such a family history. In an attempt to make an extreme comparison, the family histories of the subjects with a very high response to the cold-pressor test and those with a very low response were compared in the same way. There were thirty-four subjects with a systolic response of 25 mm. or more and a diastolic response of 25 mm. or more, and for convenience we have called them "high hyperreactors." There were forty-one with a systolic response of 8 mm. or less and a diastolic response of 8 mm. or less, and we have called them "low hyporeactors." Although these two groups are small, the results show the same trend that exists in the larger groups. In the family history of ten (29.4 per cent) of the high hyperreactors and eleven (26.8 per cent) of the low hyporeactors there were one or more cases of hypertensive cardiovascular disease. It can be seen that positive family histories among parents and siblings occurred with the same frequency in both hyperreactors and hyporeactors. The results were the same, regardless of the degree of hyperreaction or hyporeaction. These figures are greatly at variance with those of Hines,[3] who found positive family histories of hypertensive cardiovascular disease in 84 per cent of hyperreactors and 17 per cent of hyporeactors.

TABLE III

COMPARISON OF FAMILY HISTORIES OF HYPERREACTORS AND HYPOREACTORS

SUBJECTS		ONE OR MORE CASES OF HYPERTENSIVE CARDIOVASCULAR DISEASE AMONG PARENTS AND SIBLINGS	
	NUMBER	NUMBER	PERCENTAGE
Entire group	350	96	27.4
Hyperreactors	104	31	29.8
Hyporeactors	246	65	26.4

All of the family histories were elicited by one of us, and exactly the same standards were applied in all cases, regardless of the blood pressure response. Our subjects, who were employed in the home office of a life insurance company, were probably more familiar with their family histories than people in general. The information was recorded as given from memory. The subjects were asked specifically as to the health, if living, or the cause of death, if dead, of each parent and each sibling, and then they were asked if their father, mother, brothers, or sisters had, or had had, high blood pressure, apoplexy, or heart trouble.

In many instances the subject knew the actual blood pressure level of the relative who had high blood pressure. Only cases of high blood pressure or of some illness which seemed likely to be the result of hypertension were counted. Sudden death caused by cardiac and cerebral accidents between the ages of 40 and 70 was considered as probably due to hypertension. If the subject could not definitely state that such an illness had occurred among his relatives, the family history was considered negative. There were a number of cases in both groups which were regarded as doubtful because the family histories showed cases of Bright's disease or heart trouble which could not be definitely classified. These cases were excluded from the positive group, but their inclusion would not have affected the result, for the proportion among hyperreactors and hyporeactors was the same.

TABLE IV

FAMILY HISTORY AND RESPONSE TO THE COLD-PRESSOR TEST

SUBJECTS		MEAN RISE OF BLOOD PRESSURE IN MILLIMETERS OF MERCURY	
	NUMBER	SYSTOLIC	DIASTOLIC
One or more cases of hypertensive cardiovascular disease among parents and siblings	96	16.39±0.62	15.78±0.55
No hypertensive cardiovascular disease among parents and siblings	197	15.23±0.41	15.64±0.42

It is possible to show more clearly the irrelevancy of the family history in our series by comparing the blood pressure response among those who had a positive family history with that of those who had an absolutely negative family history. This analysis is shown in Table IV. Ninety-six of the 350 subjects had a positive family history of hypertensive cardiovascular disease among parents and siblings, and their response was 16.39 ± 0.62 mm., systolic, and 15.78 ± 0.55 mm., diastolic. Compare this with the response of 15.23 ± 0.41 mm., systolic, and 15.64 ± 0.42 mm., diastolic, among the 197 whose family history, with respect to parents and siblings, was negative. Statistically,* there was no significant difference in the response between those with a positive family history and those with a negative family history. Our observations are quite in agreement with those of Chesley and Chesley,[2] who found a response of 15.7 ± 0.42 mm., systolic, and 18.3 ± 0.42 mm., diastolic, among 214 pregnant women with a family history of cardiovascular-renal disease or diabetes in parents and grandparents, as against 14.6 ± 0.28 mm., systolic, and 17.2 ± 0.31 mm., diastolic, in 320 subjects with a negative family history. If one agrees with most au-

*The difference between the diastolic responses in the positive family history group and the negative family history group is so slight that it needs no comment. The difference between the systolic responses is 1.16 mm., which is 1.57 times the probable error in the difference of two means. Such a difference in one direction could occur fifteen times in 100 as a matter of chance, and, therefore, the difference is not "statistically significant."

thorities that the hereditary factor in essential hypertension is important, the belief that hyperreaction to the cold-pressor test indicates a prehypertensive state will have to be reconciled with these figures.

COMMENT

Since the subjects were selected at random, as far as response to the cold-pressor test is concerned, our results seem significant. The persons studied were employed in clerical capacities. They were asked to volunteer for the test, and this report covers the results on the first 350 volunteers with a normal blood pressure. There is no agreement among authorities as to what constitutes normal blood pressure. For this reason, we arbitrarily included all subjects whose basal blood pressure fell below 145 mm., systolic, and 95 mm., diastolic. Among the 350 subjects there were forty-six whose first blood pressure reading was more than 145 mm., systolic, and/or 95 mm., diastolic, although it fell below this during the observation. A trial analysis, omitting this group of forty-six, did not affect the incidence of positive family histories; therefore it was considered safe to include them. The subjects chosen for the test from among the group of volunteers were generally between the ages of 28 and 65. These age restrictions were the only form of selection we used, but here the effect of random sampling was not hampered because there was no foreknowledge of the blood pressure response.

Family histories of hypertensive cardiovascular disease can be taken in many different ways, and it is dangerous to make statistical comparisons of such histories when they are obtained by different observers. Some writers do not state just what relatives are included in their family history studies; others do not define what is meant by a positive family history. When the method of recording the family history is clearly described, as we have attempted to do, and when exactly the same criteria are applied throughout the study, it seems safe to make comparisons within the group observed. In our series the family histories were not known to us in advance, and the answers were recorded as given from memory. Our method was somewhat different from that of Hines, who obtained some of his family histories from records of the relatives themselves.

Fishberg[4] has said that "pending further evidence, it does not seem justified to regard a person as potentially hypertensive purely on the basis of a pronounced response to the cold-pressor test." Our results show nothing which would cause us to disagree with him. Dieckmann and Michel,[5] using a modification of Hines' technique on 101 subjects, and Briggs and Oerting,[6] who studied 233 subjects, have confirmed Hines' observations regarding family history and the response to the cold-pressor test. Our results in 350 cases and those of Chesley and Chesley[2] in a study of 539 subjects show no relationship between the response to the cold-pressor test and a family history of cardiovascular

disease. Together, these two groups include nearly 900 persons with normal blood pressure, and the results present a serious obstacle to the contention that hyperreaction to the cold-pressor test is an indication of a predisposition to essential hypertension. We agree with Hines that much more time must elapse before one can predict that a large number of hyperreactors will develop essential hypertension.

SUMMARY

Among 350 subjects with normal blood pressure, 29.7 per cent were found to be hyperreactors to the cold-pressor test. There was a family history of hypertensive cardiovascular disease in 27.4 per cent of the 350 cases. There was no relationship between the response to the cold-pressor test and the family history.

We are indebted to Mr. V. E. Henningsen, Assistant Actuary, for much valuable assistance in making the statistical analysis.

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THE EFFECT OF PENTOBARBITAL ON THE CARDIAC CONDUCTION SYSTEM OF THE DIGITALIZED DOG'S HEART

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WHILE studying the effect of digitalis and magnesium on the cardiac conduction system of dogs, we were impressed by the changes which occurred when some of the animals were anesthetized with pentobarbital. That anesthesia may produce physiologic changes is not an unusual observation in experimental work, but, when studied with the electrocardiogram, it is rather striking. Halsey,[1] in his investigation of the effect of atropine and amyl nitrite on the electrocardiogram of the digitalized dog, abandoned the use of sodium luminal as an anesthetic because it prevented the development of the usual digitalis action. Since his interest was primarily in producing auriculoventricular block with a fair degree of regularity with digitalis, the effects of sodium luminal were not studied further. It is the purpose of this paper to report the effect of pentobarbital on the conduction system of digitalized dogs, and, conversely, the effect of digitalis on the anesthetized dog.

The effect of digitalis on the electrocardiogram of man was first studied by Nicolai and Simons,[2] in 1909. Since then a considerable amount of work has been done which has little bearing on this paper. Those who are interested in the bibliography should consult Larsen, Neukirch, and Nielsen.[3] The literature on the effect of digitalis on the electrocardiogram of laboratory animals is equally as voluminous. Earlier investigators[4-9] reported their experiments with digitalis bodies, especially strophanthin, and observed chiefly changes in the T wave. Slowing of the rate and prolongation of the conduction time were also recorded. Halsey,[1] Robinson and Wilson,[10] and Reid,[11] who used larger doses of digitalis, demonstrated ectopic impulses, auriculoventricular dissociation, and ventricular fibrillation. For a more complete description of the effect of digitalis on the heart one must consult the excellent monograph of Cushny.[12] Not as much, however, has been done on the effect of the barbiturates on the conduction system. Remé and his associates[13] took electrocardiograms on animals during pernocton and evipan anesthesia. They noted alterations in the electrocardiograms, but attributed the changes to anoxemia rather than to the anesthetic agents. Gruber and his co-workers[14, 15] were able to produce alternate ventricular rhythm in dogs, rabbits, cats, and monkeys

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with anesthetic doses of the thiobarbiturates. In dogs the P-R interval was shortened. Betlach,[16] on the other hand, observed no significant alteration in the electrocardiograms of dogs which were under the influence of amytal and pentothal. Similar results were obtained by Kohn and Lederer,[17] who studied the electrocardiograms of dogs, cats, rabbits, and monkeys which were receiving pentothal. Only a small percentage of the animals developed abnormal rhythms, and these consisted mainly of ectopic beats and disturbances in intraventricular conduction. The authors make mention of one experiment in which strophanthin was used. This drug produced marked changes in the electrocardiogram, but, after the injection of pentothal, the curve quickly returned to normal. Hafkesbring and MacCalmont[18] studied the effect of amytal, pentobarbital, and barbital on the conduction system of dogs and cats. The only cardiac effects of anesthetic doses of each of these agents, as shown by the electrocardiogram, were an increase in heart rate and a decrease in the sinus arrhythmia which is commonly seen in dogs and cats.

Clinically, Betlach[19] was unable to demonstrate changes in the electrocardiograms of hypertensive patients who had received sodium pentothal. Volpitto and Marangoni[20] were in agreement; they were unable to detect any changes in seventeen cases of pentothal, thioethamyl, and evipal anesthesia.

METHODS

The unanesthetized dog was placed on the left side, and electrodes were attached to the right front and left rear legs (conventional Lead II). The dogs had been previously trained to lie quietly. Electrocardiograms were made with a string galvanometer type of instrument. All of the drugs were injected into the right saphenous vein.

Observations were made on seventeen dogs. Pentobarbital was selected arbitrarily because its action is short and it is frequently used in animal experimentation. The pentobarbital was administered in a 10 per cent alcoholic solution; each cubic centimeter contained 1 gr. (0.06 Gm.). At no time did the dosage exceed that usually required to produce surgical anesthesia, namely, 1 c.c. per 5 pounds of body weight. It was noted that less pentobarbital was needed to produce anesthesia in the digitalized than in the nondigitalized animal. The anesthetic was administered slowly (2 c.c. per minute), and discontinued when the corneal reflexes were abolished. The digitalis was given in the form of digalen; 2 c.c. were equivalent to 1 cat unit. It was administered rapidly in large doses, ranging from 1 to 1⅓ cat units per kilogram of body weight. This dosage was found adequate to consistently produce a marked digitalis effect.

RESULTS

Experiment I.—In this experiment fourteen studies were made. Control electrocardiograms were taken and digitalis was administered. The maximum digitalis effect was usually noted within thirty minutes,

at which time the pentobarbital was administered. In all but three experiments the observations were terminated within forty-five minutes after anesthesia. In the three exceptions the dogs were studied until consciousness returned. Electrocardiograms were taken at five-minute intervals.

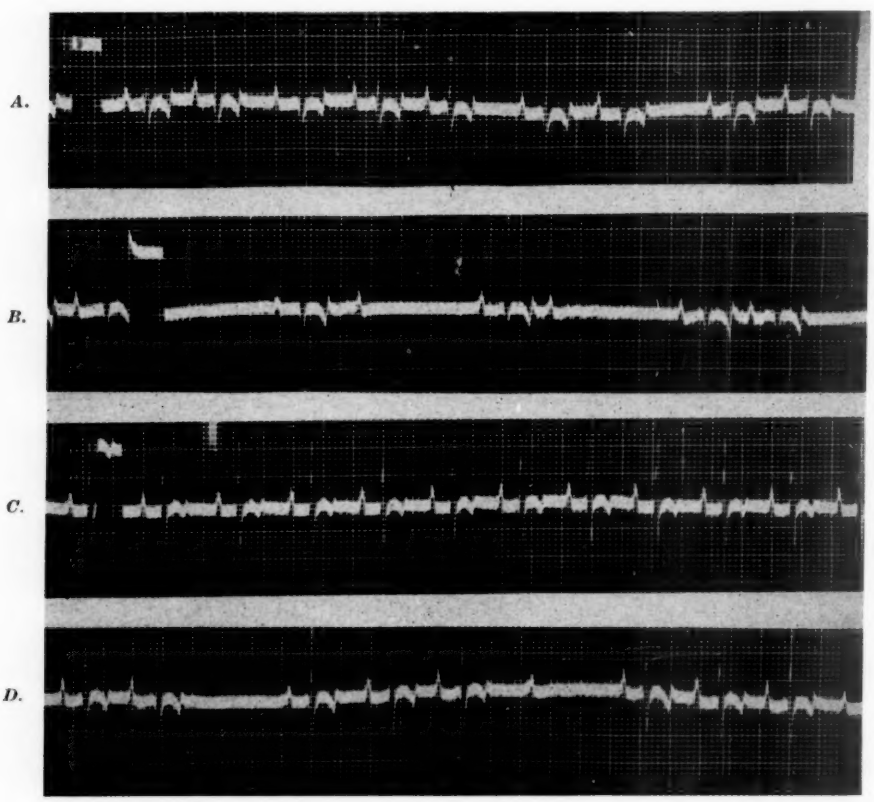

Fig. 1.—*A*, Normal. *B*, After the administration of digitalis (1½ cat unit per kilogram). Complete A-V block. *C*, After the administration of pentobarbital. *D*, Twelve hours later. Residual digitalis effect still noted.

Ten (71.4 per cent) of these dogs responded to digitalis in the following manner (Fig. 1). The rate became slower by 20 to 40 beats, and the auriculoventricular conduction time increased by 0.02 to 0.04 second. In 60 per cent, partial or complete auriculoventricular block occurred. Nodal or auricular premature contractions were common. Blocked premature auricular systoles, as described by White and Sattler,[21] were noted. Ectopic impulses of ventricular origin were uncommon except in one experiment, in which alternating ectopic impulses of ventricular origin developed (Fig. 2). Sinus arrhythmia, which is so common in dogs, was seldom abolished, and T-wave changes were inconsistent.

When pentobarbital was given to the ten dogs mentioned above, two types of reactions occurred. In five animals the rate immediately became regular and more rapid and always exceeded the control rate. The P-R interval, which had been lengthened by digitalis, became shorter, and in some animals was less than the control measurement. In the remaining five dogs, pentobarbital produced an ectopic tachycardia of ventricular origin (Fig. 3). In one dog the ventricular tachycardia was produced only after additional pentobarbital was given; the smaller doses caused sinus tachycardia.

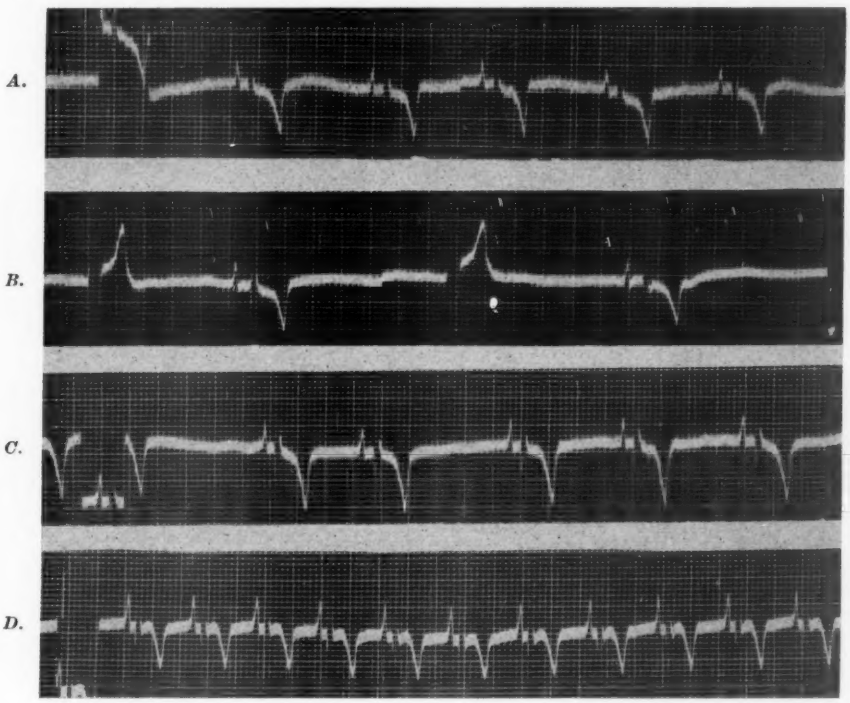

Fig. 2.—*A*, Normal. *B*, After the administration of digitalis. Note alternating ectopic impulses of ventricular origin. *C*, After the administration of pentobarbital. Sinus rhythm with increase in auriculoventricular conduction time. *D*, Twelve hours later.

In the dogs which were studied until they became conscious, the electrocardiograms revealed sinus mechanism, with a residual digitalis effect.

When digitalis was administered to the four remaining dogs in this group, an ectopic tachycardia of ventricular origin developed (Fig. 4). The ventricular rate was usually 175 or more beats per minute, and two to five times as rapid as the auricular rate. The ventricular and auricular impulses were irregular, indicating not only independent rhythms, but also numerous ectopic foci in both auricles and ventricles. In this group pentobarbital had little effect except that of increasing the auricular rate.

Experiment II.—In this experiment three dogs were studied. They were first anesthetized with pentobarbital, and then given digitalis. After the administration of pentobarbital a definite increase in heart

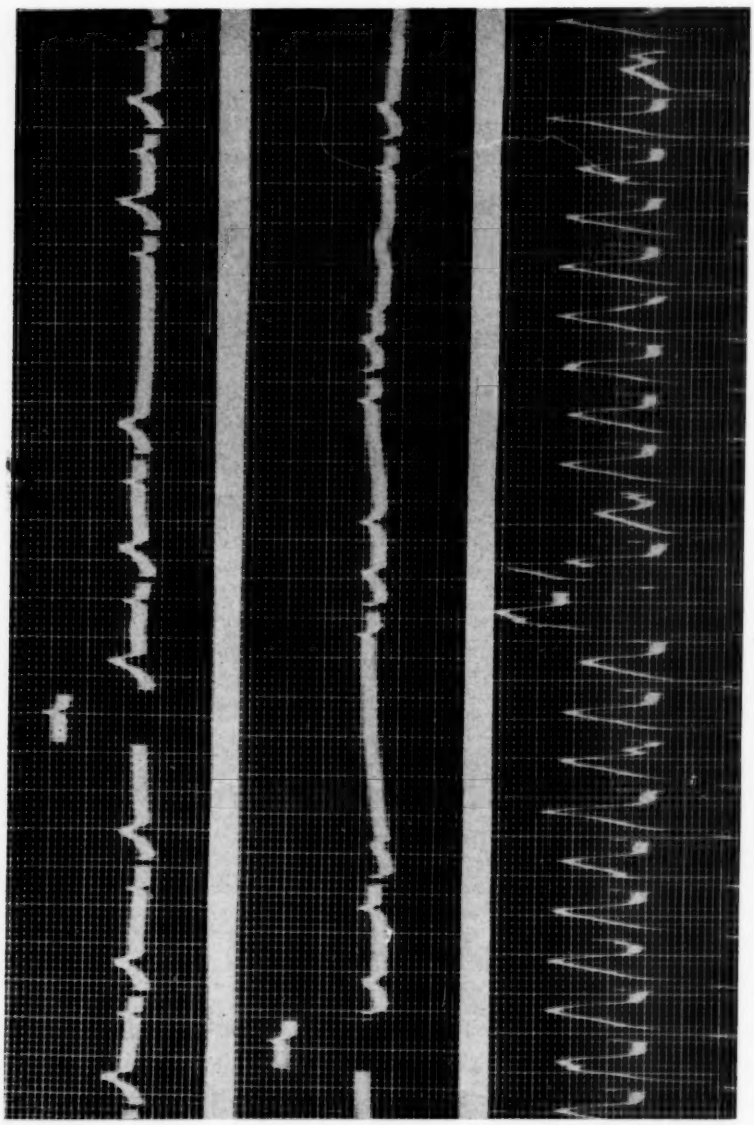

Fig. 3.—*A*, Normal. *B*, After the administration of digitalis. Usual digitalis effect noted. *C*, After the administration of pentobarbital. An ectopic tachycardia of ventricular origin was produced.

rate was noted. In two of the three dogs the auriculoventricular conduction time decreased 0.02 and 0.04 second, respectively. Pre-existing sinus arrhythmia was invariably abolished. These were the only changes. After the dogs were anesthetized, digitalis was administered in doses similar to those used in Experiment I, and its effect was found to be different from that on the unanesthetized dog. In the

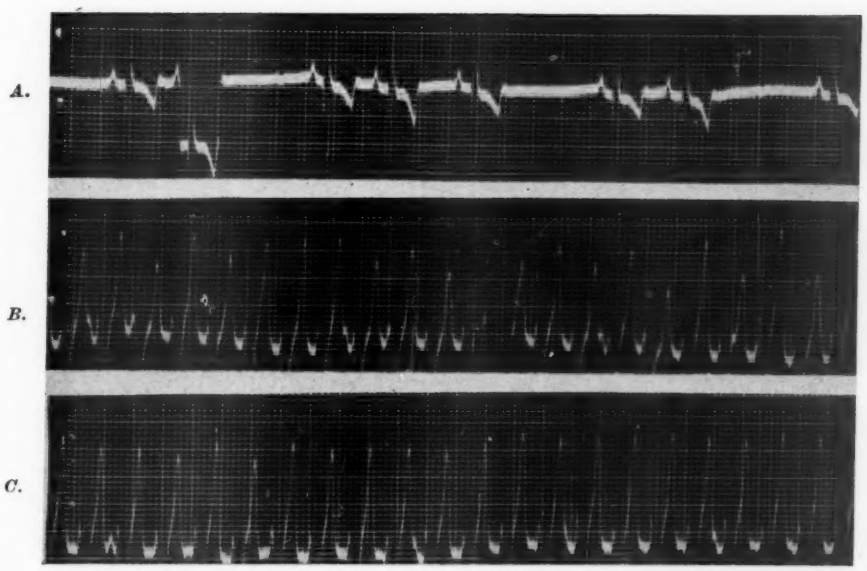

Fig. 4.—*A*, Normal. *B*, After the administration of digitalis. *C*, After the administration of pentobarbital. The ectopic tachycardia of ventricular origin remains unchanged.

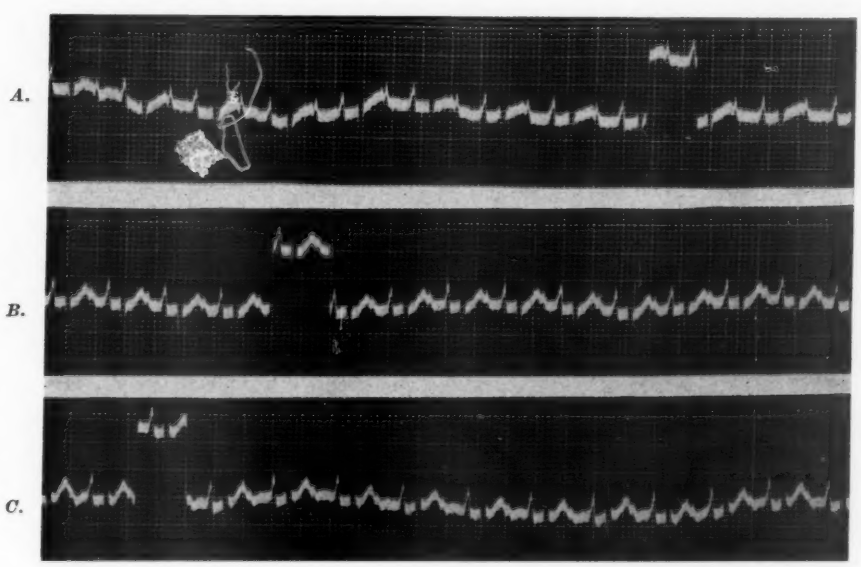

Fig. 5.—*A*, Normal. *B*, After the administration of pentobarbital. Note increase in rate and slight increase in auriculoventricular conduction time. *C*, After the administration of digitalis. Curve remains essentially unchanged.

first dog (Fig. 5) digitalis had no effect on the conduction system, as shown by the electrocardiogram. When this dog had been used in Experiment I, a typical digitalis effect occurred.

In the second dog, digitalis had produced, in Experiment I, alternating ectopic impulses of ventricular origin which were abolished by pentobarbital (Fig. 2), but in this experiment digitalis was capable only of slowing the rate and slightly prolonging the P-R interval (0.02 second). An electrocardiogram which was taken three hours later, after the dog regained consciousness, was not unlike the control except as to rate.

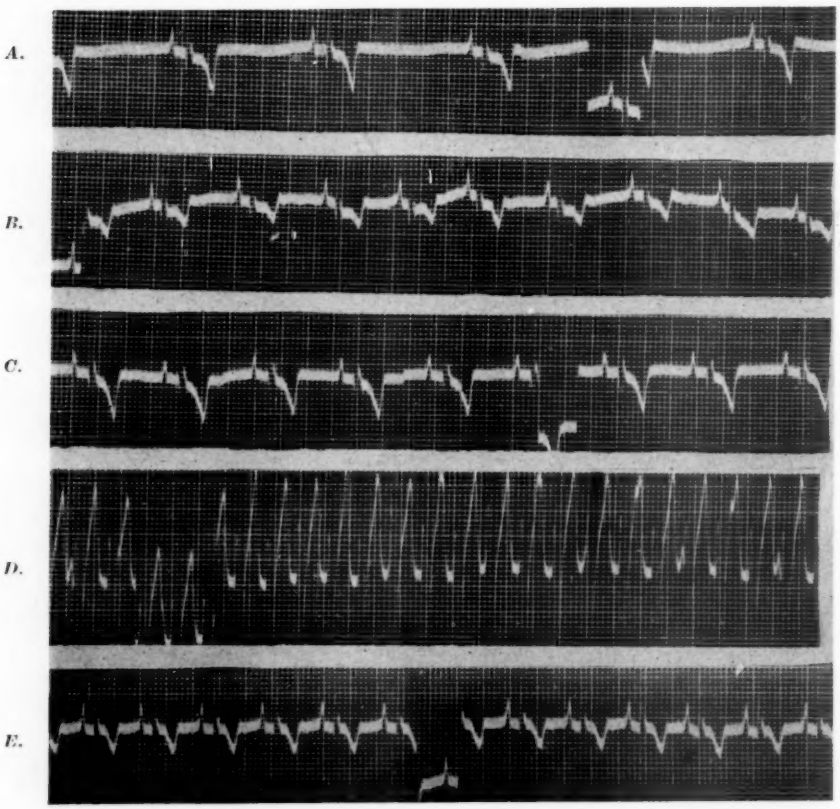

Fig. 6.—*A*, Normal. *B*, After the administration of pentobarbital. *C*, After the administration of digitalis. *D*, Ten minutes after the administration of digitalis. *E*, Four hours later. The dog was now awake.

After the administration of digitalis to the third dog, the rate became slower, and the auriculoventricular conduction time was prolonged. Within ten minutes, ectopic tachycardia of ventricular origin developed (Fig. 6). The latter did not occur when this animal was used in Experiment I. Electrocardiograms were taken four hours later, when the dog was again awake, and revealed sinus tachycardia with a normal P-R interval.

COMMENT

The action of digitalis on the conduction system is well known and need not be discussed. The same cannot be said of the barbiturates. De Waele[22] reported vagus nerve depression from the effects of a mixture known as "Somnifene." In 1929, Lieb and Mulinos[23] called attention to the depressant and paralytic action of amytal on the cardiac vagus mechanism of the rabbit, cat, and dog. Garry[24] confirmed these observations and added the conclusion that amytal not only depresses, but, in some instances, completely paralyzes, the peripheral vagal ganglia. Since acetylcholine continued to be active during the period of amytal action, he concluded that the postganglionic fibers of the vagus were still responsive. He found that amytal was most effective on the vagus, whereas, in ordinary doses, phenobarbital was not effective at all. Shafer, Underwood, and Gaynor[25] studied the effect of sodium amytal on etherized, as well as decerebrated, dogs. In their decerebrated animals, amytal impaired the effect of vagus stimulation on the heart, and this depression could be surmounted by prolonged faradic stimulation of maximum strength. They observed some recovery of the vagus from the impairment, but in no case was the original, full, vagus inhibitory effect upon the heart regained, even after five hours of rest.

These observations were confirmed by Linegar, Dille, and Koppanyi.[26] In addition, they demonstrated that the effectiveness of different barbiturates varies considerably, in that amytal, pentobarbital, and pernoston are effective in moderate doses, whereas barbital was effective only when the doses were relatively enormous. Pilocarpine, when administered intravenously, was capable of diminishing, or even abolishing, this effect, which suggests that the action of the barbiturate on the vagus nerve was similar to that of nicotine and curare, rather than atropine. Phenobarbital had no demonstrable depressant effect. Swanson and Shonle[27] failed to demonstrate vagal depression with pentobarbital, but they used inadequate doses. Gruber and his associates[28] showed that barbiturates, when applied directly to the heart, produce paralysis not only of the ganglia, but also of the nerve endings.

It appears reasonable to assume that pentobarbital, since it has a depressant effect on the peripheral vagus ganglia, is capable of neutralizing the vagal action of digitalis. Atropine, which has a similar action, is capable of doing this. It is interesting to note the similarity between our results and those of Halsey,[1] who studied the effect of atropine on the conduction system of the digitalized dog. As long as the vagus is able to influence the various cardiac structures which are capable of initiating impulses, particularly the sinoauricular node, pentobarbital should be able to alter the effect of digitalis. This was found to be true in the early stages of digitalis intoxication, for pentobarbital abolished the usual bradycardia, auriculoventricular block, and premature con-

tractions. In the later stages of digitalis intoxication, when the ventricles became sufficiently irritable to produce an ectopic tachycardia, with complete dissociation between auricles and ventricles, pentobarbital was no longer capable of altering this rhythm except by increasing the auricular rate. Occasionally, pentobarbital appears to facilitate or bring about the occurrence of an ectopic tachycardia of ventricular origin in a heart which shows a moderate digitalis effect.

SUMMARY AND CONCLUSIONS

1. The effect of pentobarbital and digitalis on the conduction system of dogs was studied by means of the electrocardiogram.

2. Pentobarbital was found to alter the function of the conduction system in the digitalized dog.

3. Changes produced by digitalis, such as bradycardia, partial or complete auriculoventricular heart block, and ectopic impulses of ventricular origin, were abolished in five dogs by pentobarbital. In five other dogs pentobarbital produced ectopic tachycardia of ventricular origin.

4. When the ectopic tachycardia of ventricular origin was produced initially by digitalis, pentobarbital had no effect except to increase the auricular rate.

5. When digitalis is given to the dog which is anesthetized with pentobarbital, the usual digitalis response may not be elicited.

6. The action of pentobarbital on the conduction system is probably the result of its depressing effect on the vagus.

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ERGOGRAPHIC STUDIES

Description of a New Device, and Observations on Normal Subjects and on Patients With Intermittent Claudication

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INTERMITTENT claudication, which may be defined as symptomatic evidence of an inadequate blood supply to active muscle, is the earliest symptom in 51 per cent of all cases of thromboangiitis obliterans.[1] Often it may be the only clinical sign of occlusive arterial disease, and it may appear long before trophic lesions become manifest.

Although a great many methods are used to obtain qualitative and quantitative information about the blood flow through the skin,[2, 3] there are not many ways of estimating the supply of blood to the muscles in man without surgical intervention. Foster[4] and Silbert[5] described and used special thermocouples which, when inserted into the muscle belly, recorded changes in temperature; these changes were interpreted as indicating variations in the blood supply of the muscles. By this means, Silbert demonstrated the effect of certain drugs and various other procedures on the temperature of the muscles. This method, however, cannot be applied to active muscle, and is not ideal for general clinical work. Moreover, it remains to be demonstrated that this is a reliable method of ascertaining blood supply to muscles under any circumstances. Other authors (e.g., Pearl[6]) approached the problem by studying the changes in the skin temperature of the digits and using these changes to draw conclusions concerning the blood supply to the muscles of the extremity. Knowing that "it is no longer justifiable to conclude that an evident increase in the circulation of the skin is accompanied by a similar increase in the underlying muscles,"[2, 3, 5] it also appears unjustifiable to base conclusions about circulation in muscles on the presence or absence of skin temperature elevation after vasomotor paralysis, for these studies may indicate the status of the skin circulation only. A rise in skin temperature does not necessarily bear a definite relation to the amount of blood reaching the muscles. Elevation of the digital temperature as a result of peripheral nerve block seems to me to be neither sufficient reason for excluding the possibility

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of organic obstruction of the vessels supplying the regional muscles, nor sufficient justification for designating the cause of the claudication in such a case as "vasospastic."

In the literature of peripheral vascular disease, one usually finds the degree of intermittent claudication described in the following noncommittal manner: "the patient states that after walking three blocks he experiences pain." Naturally, the patient's own account of his symptoms is vitiated by various factors, such as differences in speed and gradient, and is thus of small value. Barker, Brown, and Roth[7] therefore estimated the degree of intermittent claudication by having the patient walk on the level at a standard speed.

Instruments designed to measure muscular work have been known as ergographs ever since Mosso[8] devised such an apparatus to study fatigue of the muscle of the middle finger and other related problems. Since fatigue of normal muscle is mainly a function of its blood supply, such methods may well be used for the study of the latter, and, in a number of instances, this has been done (Lewis, Pickering, and Rothschild,[9] Ratschow,[10] Simmons,[11] Hitzrot, et al.,[12] and Fisher, et al.[13]). I have constructed an ergograph which can be used to investigate the blood supply to the muscles of the lower extremity.

APPARATUS*

Ratschow's and Simmons' apparatus consists mainly of an inclined foot splint, serving as a support for the leg, on which an upright foot piece is fixed by means of a pair of hinges. The axis around which the plantar or dorsal flexion of the foot normally takes place passes through the malleoli, and not through the end of the calcaneus, to which the hinge in such an apparatus corresponds. Furthermore, with such an arrangement the subject cannot control his movements, and therefore the weight is lifted to various heights by different subjects, which gives uncomparable results. No tracing can be obtained. The ergograph which has been employed in our studies differs in many respects from any other type in use for the lower extremities. It consists mainly of four parts (Fig. 1*A* and *B*), namely, the ground board (*G.B.*), upon which are fixed the support for the leg (*L.S.*), the foot piece (*F.P.*), and the upright board (*U.B.*). The shape of the leg support, which is fitted at a height of 10 cm., inclines somewhat toward the foot piece. Special care was taken in constructing the foot piece (*F.P.*), upon which the adjustable foot piece proper (*F.P.p.*) is fixed with two bolts which slide in slits (*S*) to allow adjustment of *F.P.p.* The foot piece proper is fitted with a heel and toe cap and two leather belts to fix the foot of the subject. The foot board (*F.P.*) is suspended in such a way that it can easily be moved around an imaginary axis passing through the joints *A* and *B* and through the malleoli of the foot when it is fixed on the foot board. It is this suspension of the foot piece which enables the foot to rest comfortably and firmly, with its whole surface upon its support, during the movements. A screwing bolt (*Bt*) permits adjustment of the amount of initial plantar flexion, and a string with a screw fixed on both *F.P.* and *U.B.* enables one to adjust the initial amount of dorsal flexion. The upright board, *U.B.*, is fitted with a metal

*I am indebted to Mr. G. McManus, laboratory assistant in this department, for his valuable help and suggestions during the construction of the apparatus.

arm, *M.A.*, bearing pulley *1*, the scale, and several pulleys (*2*, *3*, *4*, *6*, *7*, and *8*) which are partly fitted in openings of the board to guide the various strings. The upright board is kept in place by a triangular piece (*T.P.*) which has a square opening to take the screw wheel (*S.W.*) to bolt *Bt*. It also holds pulley *5*. Two strings (*X* and *Y*, Fig. 1) are attached at the end of the foot board, both of which, after running over a number of pulleys, lead to the weight (*W*) gliding up and down in a cage (*C*). Depending upon which group of muscles is to be tested,

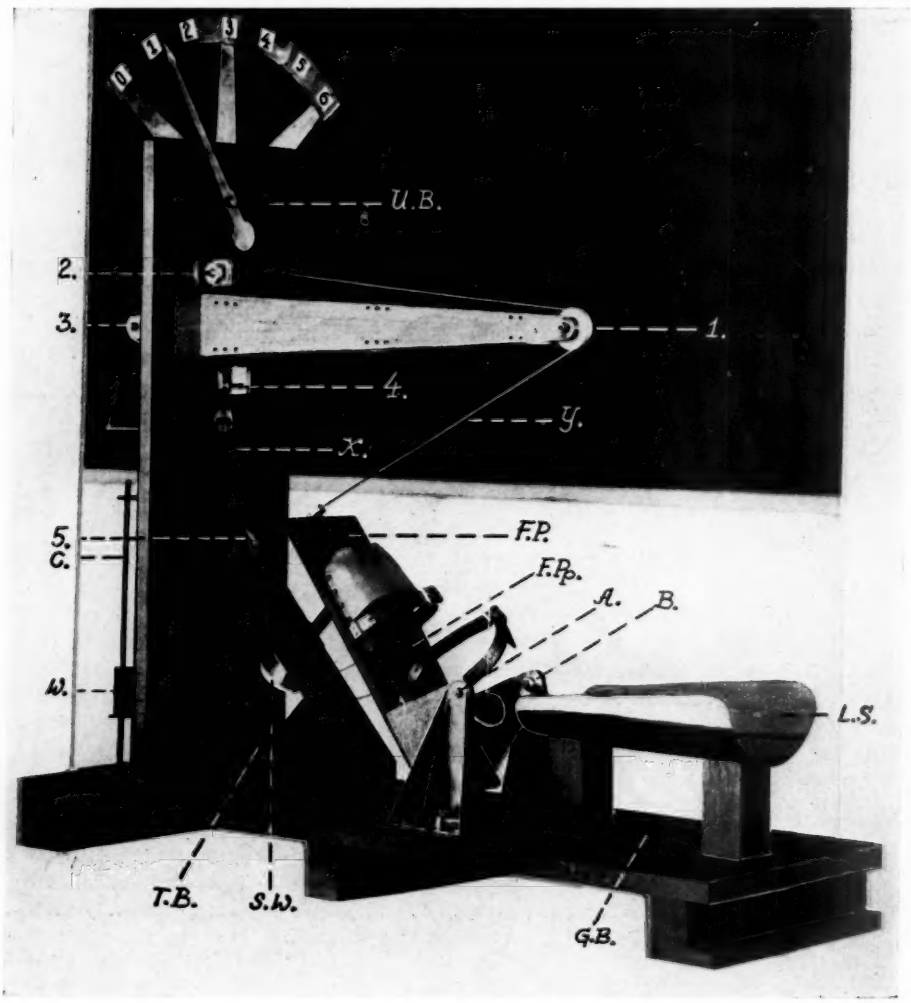

Fig. 14.—Ergograph for ascertaining the claudication index in the lower extremity.

either dorsal or plantar flexion of the foot will be required. For dorsal flexion (anterior tibial group), string *X*, leading from *F.P.* over pulleys *5*, *4*, and *3* to the weight, will be used. For plantar flexion, string *Y*, leading from *F.P.* over pulleys *1*, *2*, and *3*, will carry the weight. The indicator on top of *U.B.* is worked by string *R*, leading from the side of the foot board over pulley *7* to pulley *8*. In the same way, string *Q* is fixed at the side of *F.P.*, runs over pulleys *6*, *9*, and *10*, and works

a lever on the paper of a kymograph. With *Q* and *R* fixed at different heights on the side of *F.P.*, the excursion of both the indicator and the recording lever can be adjusted within wide limits.

The subject rests upon a bed in a half-reclining position. The upper part of the leg is bent in an angle of 120° against the body, and the lower and upper parts of the leg form an inner angle of approximately 135°. The leg to be investigated is fixed in the ergograph, and, during the test, the subject moves his foot according to the beat of a metronome.

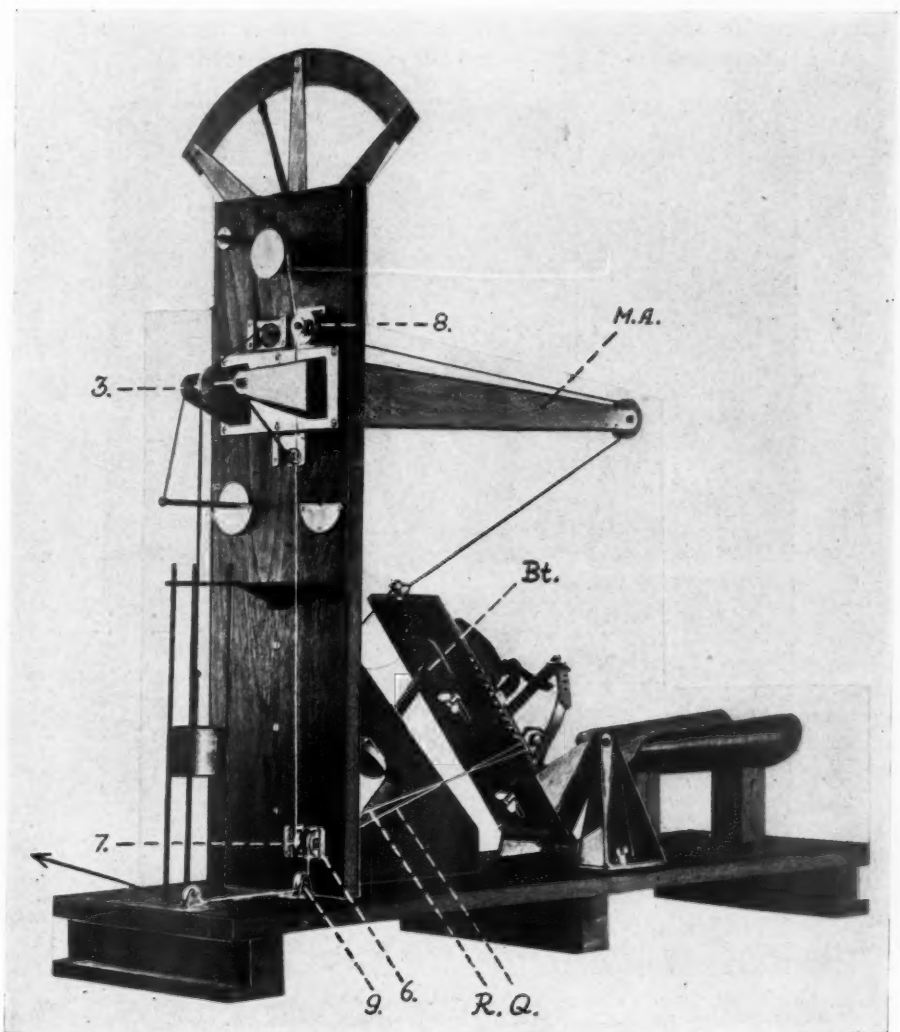

Fig. 1*B*.—Ergograph for ascertaining the claudication index in the lower extremity.

RESULTS

When a person with either a normal or an impaired arterial circulation performs dorsal or plantar flexion of his foot, thereby elevating a

given weight, his muscles soon tire, but this does not prevent his flexing the foot to the original extent. If he continues the work, pain develops, and, with further exercise, becomes so severe that full flexion is impossible. Eventually, he is compelled to give up the exercise completely (Fig. 2*A* and *B*). The pain vanishes within a few seconds after stopping the exercise, and a dull aching and sense of heaviness persist for some time. Paresthesia may be experienced. Patients who have intermittent claudication in one leg, and exercise the "unaffected" leg first, describe the pain as being exactly of the same character as that which they experience in the affected leg when they walk.

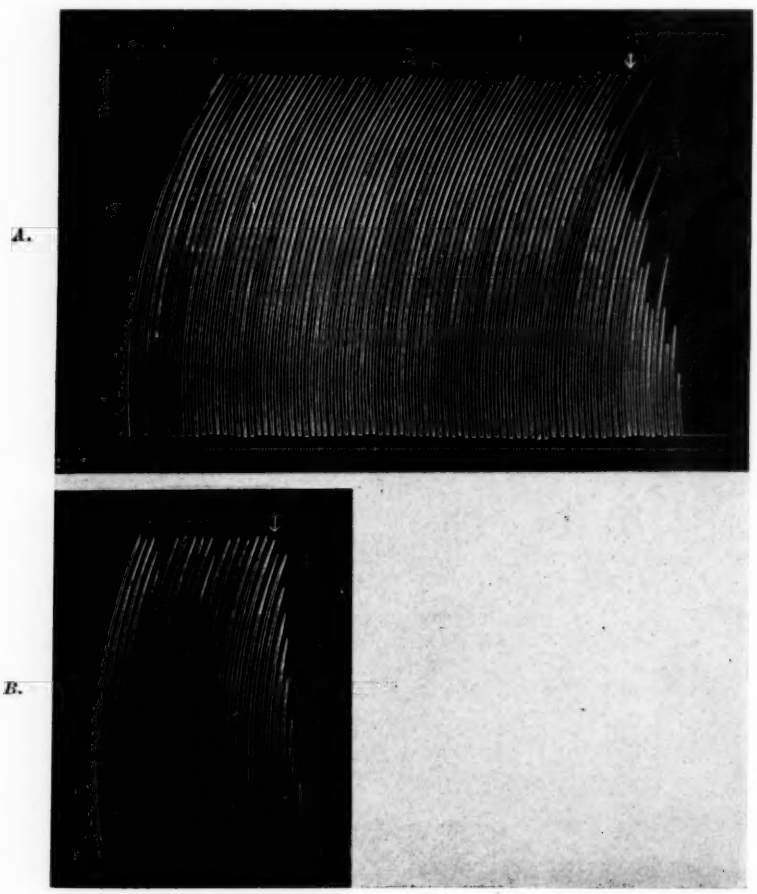

Fig. 2.—Ergograms of a normal subject (*A*) and of a patient with advanced thromboangiitis obliterans (*B*). Fifteen hundred grams lifted 25 cm. by dorsal flexion.

The results of all ergographic studies, if voluntary contractions are recorded, depend upon the volition of the subject.* We tried to overcome this difficulty by arranging the indicator, with its scale, on top of

*The results of investigations in which the muscles were electrically stimulated in order to exclude the volition of the subject will be dealt with in another publication.

the apparatus, so that the subject could control his movements. In this way it was also possible to obtain the same elevation of the weight in all cases by asking the subject to move only between two given marks on the scale.

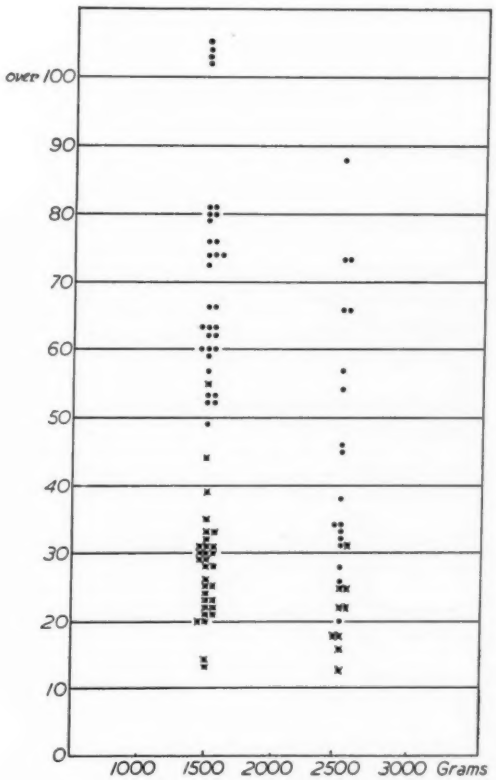

Fig. 3.—Claudication indices of normal legs (dots) and abnormal legs (crossed dots) after lifting 1,500 Gm. and 2,500 Gm., respectively, to a height of 25 cm. by dorsal flexion.

All previous authors have used either the total amount of work of which the muscles were capable, or the time of onset of pain, for evaluation of the results; this introduces a subjective factor in ascertaining the end point. Investigation has taught us that the time of onset of the pain depends much upon the subject, and what he considers worth noticing. It was found to be a reliable criterion only when various results on one subject were compared. Comparable results on different subjects were obtained by counting the number of complete contractions, rather than by measuring the amount of work performed or observing the time of onset of pain. Naturally, the number of full contractions will be dependent upon the amount of work performed, and this, in turn, will depend on the height to which the weight is lifted. If the number of contractions are plotted against the various heights to which the weight has been lifted, a paraboliform graph is

obtained. In Fig. 3 the values obtained on twenty-five normal and forty abnormal subjects have been plotted against two different heights; all other conditions were identical. Elevating 1,500 Gm. results in a distinct distribution of the indices of both the normal and the abnormal subjects. This gives way to considerable overlapping if the weight is increased to 2,500 Gm. Weights of less than 1,500 Gm. did not regularly exhaust the muscles. From this it is apparent that, in our experiments, using a weight of 1,500 Gm. gave significant results. For dorsal flexion, the optimum weight was 1,500 Gm. (lifted 25 cm.), and, for plantar flexion, 7,000 Gm. (lifted 25 cm.). One and one-half seconds for contraction, alternating with one and one-half seconds for relaxation, was the rhythm which was found to be most reliable. The number of full contractions which was obtained under these standard conditions was used in all subsequent experiments as a criterion and is referred to as the *claudication index.*

DISCUSSION

Starting from the fact that the efficiency of muscular work is to a large extent a function of the blood supply, the ergographic methods which are usually employed for physiologic investigation of muscular fatigue may be successfully applied in the study of the muscular ischemia which causes intermittent claudication. The method may be used to differentiate other forms of pain in the legs (caused by neuritis, flat foot, arthritis, and varicose veins) from intermittent claudication, although the experienced clinician seldom needs such help. Valuable objective information concerning the effect and progress of therapy may be obtained, especially in cases in which no trophic lesions are present. The advantage of having a record for further reference is substantial.

THE CLAUDICATION INDEX OF THE NORMAL SUBJECT UNDER ORDINARY LABORATORY CONDITIONS

As stated previously, it has been found that the most reliable criterion of blood supply to muscle is obtained by counting the number of full contractions, rather than by estimating the total amount of work of which the muscles are capable. This index, which is obviously proportional to, if not identical with, the walking capacity of the patient, is called the "claudication index."

This claudication index depends not only on the amount of work being performed, but also on certain intrinsic factors, of which the development of the muscles and the age and general psychic state of the subject are important. Therefore, there is a considerable range in the values of the claudication index among normal subjects, even if the material which is used appears to be homogeneous. From Fig. 4, which gives the distribution in the group of normal persons, it is evident that, in thirty-six

of thirty-seven subjects (97 per cent), the claudication index was above 50, and that, in thirty-three subjects (84 per cent), it fell between 50 and 90. In only one clinically normal person (52 years of age) were the indices for one leg found to be constantly in the 40 to 50 range. Values considerably higher than 90 were observed in three instances. Thus it appears that any index below 40 must be considered definitely abnormal. The indices for the two legs are usually within the same range, regardless of whether the subject is right- or left-handed. However, when marked differences were observed, the higher value was regularly found in the right leg of right-handed persons, and vice versa. The results were very constant, even when the observations were made at intervals of as much as a year or more. No definite relation between the indices and vasomotor tone could be detected, but this will be the subject of further study.

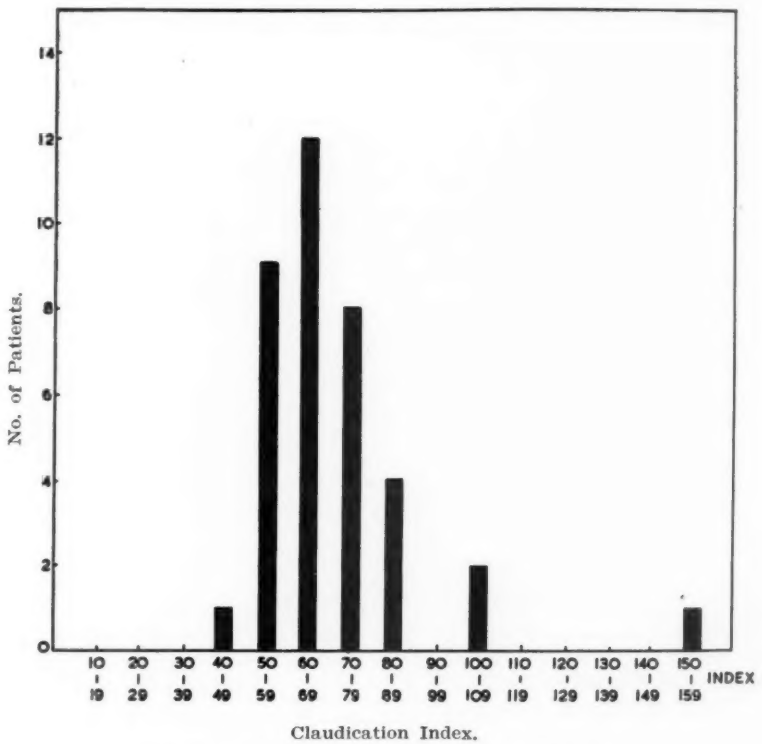

Fig. 4.—Claudication index in normal subjects.

THE CLAUDICATION INDEX IN CASES OF CHRONIC, OCCLUSIVE, ARTERIAL DISEASE

Thirty-eight patients with intermittent claudication were studied; twenty-six had thromboangiitis obliterans, and twelve had arteriosclerosis obliterans. Not only is there a marked diminution of the

claudication index in occlusive arterial disease, depending, naturally, upon the degree of the pathologic changes, but there is also a very steep decline after the last full contraction. It has been found that indices taken on different occasions are extraordinarily constant. The indices

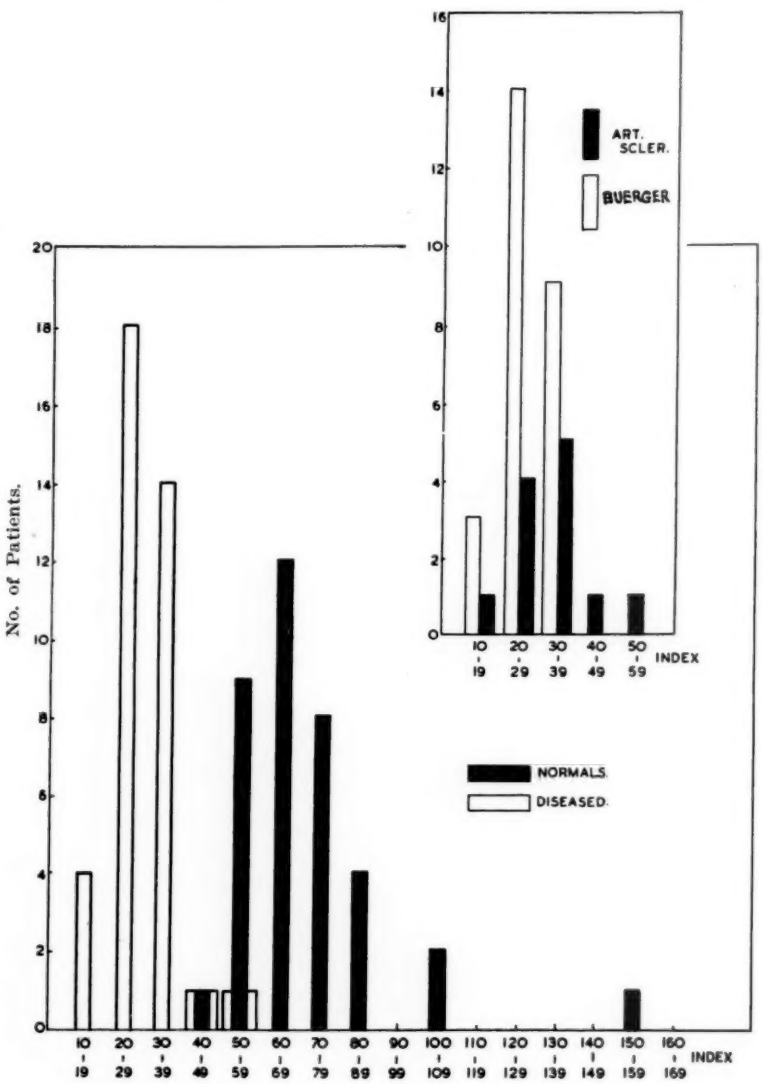

Fig. 5.—Claudication indices in cases of intermittent claudication.

in thirty-six of thirty-eight (95 per cent) of our cases were below 40, with a peak in the 20 to 30 range (Fig. 5). In two cases of arteriosclerosis obliterans, associated with a mild degree of intermittent claudication, in which there was a good collateral circulation, as judged

by the skin temperature and plethysmographic measurements, the claudication index was above 40. In the case in which the indices on the two sides were 56 and 58, respectively, the complaint was more of fatigue,

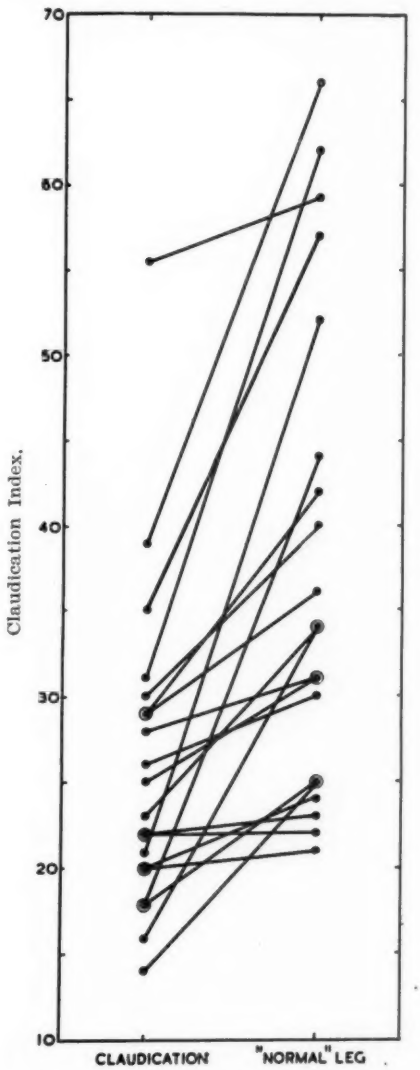

Fig. 6.—Relation between the claudication indices of the two legs of patients with a history of intermittent claudication in only one leg.

after a walk of about one mile, than of real pain. It has been found that the index is usually in close agreement with the severity of the clinical manifestations. The shorter the walking distance until claudication appears, the lower the index. On the other hand, it could be proved that, in cases in which the claudication was supposed to be severe, but the claudication index was high, the history did not correctly portray

the true state of affairs. There is no definite difference in the range of the claudication indices in thromboangiitis obiterans and arteriosclerosis obliterans (Fig. 5).

Although the patients usually complained of claudication in one leg only, the other leg, in many cases, especially when the disease was severe, also showed a reduced index, indicating bilateral involvement which was not apparent clinically (Fig. 6). Only in a small group of cases was the index of the unaffected leg still within the normal range (above 50); in most cases it was distinctly reduced. It may therefore safely be concluded that the circulation in the "unaffected" leg is usually already considerably impaired, an observation which in most, if not all, cases could be confirmed by other methods. It is only because exhaustion of the more affected leg takes place first, and forces the patient to stop, that the impairment of the circulation in the "unaffected" leg does not become obvious during walking. Often there is a difference of only 5 to 6 in the claudication indices of the two legs, but this is sufficient to make the claudication unilateral. As shown in Fig. 5, in most of the cases of moderate claudication there is a bigger difference between the indices of the two legs if one leg still has normal, or almost normal, values. As the occlusive process progresses, the indices in the two legs are found to be more and more within the same range, until the originally less affected or unaffected leg may appear worse than the one which was involved first. As the disease advances, the claudication index decreases until, in the patients with rest pain, it becomes almost zero. This decrease can be followed up. In one case of thromboangiitis obliterans a year elapsed between the tests; the index decreased during that time to almost half its original value, indicating further impairment in the blood supply to the regional muscles. This agreed well with the history, which was to the effect that the condition had become much worse during that year.

THE CLAUDICATION INDEX AFTER EXPERIMENTAL ARTERIAL OCCLUSION

That the onset of claudication and the height of the claudication index are dependent upon the blood supply of the muscles can be readily demonstrated by experiments in which the arterial blood supply to the exercised limb has been stopped suddenly (Fig. 7). Thus the conditions which obtain in disease can be simulated in the normal subject. The claudication indices of the normal subject after arterial occlusion are not only greatly reduced, but agree remarkably well with those in cases of severe intermittent claudication. In cases of advanced claudication, in which there are a low index for the leg concerned and a relatively high one for the unaffected leg, experimental arterial occlusion will reduce the index for the unaffected leg to a value within the same range as that recorded for the diseased leg. The low indices in cases of severe

claudication might therefore be regarded as indicative of almost complete arterial occlusion in the region of the muscle which becomes painful. However, the amount of blood trapped in the leg by the cuff which is used to produce experimental arterial occlusion may supply a considerable amount of oxygen, and therefore the assumption in the foregoing sentence might well be false. Normally there is a big difference between the claudication indices before and after experimental arterial occlusion, but this is not true of the abnormal leg. In cases of advanced occlusive arterial disease the difference is very small. The difference between the indices before and during experimental occlusion may therefore be used as a rough measure of the circulatory reserve in the region of the exercised muscle. The bigger the difference, the less obstruction and the more circulatory reserve. With an advanced degree of obstruction there is less circulatory reserve, as indicated by a small difference between the two values. It may be mentioned that, when the claudication index of the nonaffected leg was ascertained during experimental occlusion, the patients regularly volunteered that the pain in that leg during the procedure was absolutely identical with that experienced in the affected leg after walking.

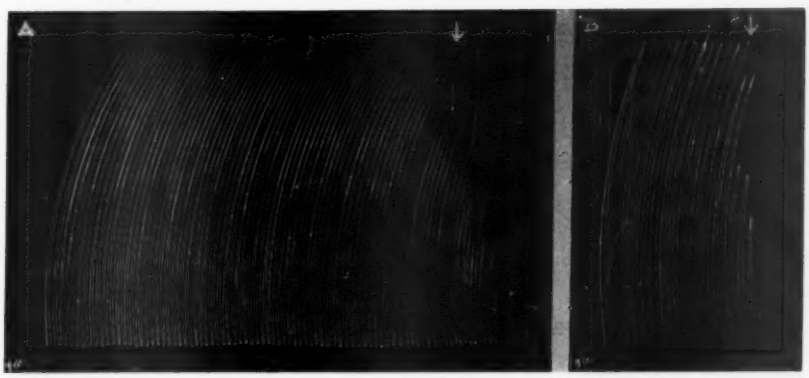

Fig. 7.—Effect of experimental arterial occlusion on the claudication index of the normal subject. *A*, ergogram before, and *B*, ergogram after, inflating a cuff above the knee to 200 mm. Hg (blood pressure, 120/65).

EFFECT OF TREATMENT

A report of the effects of various kinds of treatment on the claudication index will be given in another communication. Preliminary studies indicate that repeated intravenous injections of a hypertonic solution of sodium chloride, as recommended by Silbert,[5] increase the claudication index.

DISCUSSION

There may be some difficulty in making the diagnosis of obliterating disease of the arteries, especially in cases in which the clinical manifesta-

tions are not very pronounced, e.g., when trophic lesions are absent, there is no diminution in the size of the pulses, and the roentgenograms do not show any calcification. The clinical picture in such cases may be suggestive of a great number of conditions, although a careful history enables one to exclude most of them. In some of these cases, measurement of the skin temperature may reveal a diminished response to the ablation of vasoconstrictor influences, indicating obstruction of the skin arterioles. It may be justifiable in some of these cases to assume that there is a similar occlusion of the muscle vessels. However, in many cases, early in the disease, the skin temperature may still be normal, and this might be taken to mean that the blood supply to the muscle was normal. This conclusion is, however, unwarranted. A normal response of the skin temperature to vasoconstrictor paralysis does not prove that there is a normal cutaneous circulation, as has been clearly demonstrated.[14] More sensitive methods can easily detect marked pathologic changes in many cases in which, as judged by skin temperature readings only, the circulation would be regarded as normal. Therefore, quite apart from the fact that it is questionable whether one may be permitted to draw conclusions concerning the blood supply to the muscles from any method of measuring the circulation to the skin, a normal response of the skin temperature is an inferior criterion of the patency and efficiency of the circulation. Indeed, there were cases in which the high claudication index which was obtained showed no relation to the severity of the trophic lesions that were present.

The ergographic method of estimating the blood supply to active muscle has the definite advantage of being able to furnish a quantitative index of the blood flow through the muscle only. After having standardized the work to be performed by each subject, and using the number of full contractions (the so-called claudication index) as a criterion, we found the indices to be above 50 in 97 per cent of the normal subjects. The indices in the limbs in which there was intermittent claudication were below 40 in 95 per cent of the cases, and in only two of thirty-eight cases were they above 40. Thus there were little overlapping and a distinct range for both the normal and abnormal extremities.

It is in the cases of early involvement that a diminished claudication index may provide valuable objective evidence of arterial obstruction. In cases of severe claudication, other signs of arterial insufficiency will make the diagnosis of arterial obstruction easy, and special investigation will not be necessary. However, it is in these cases that more information about the vascular reserve is needed in order to give a prognosis. An estimation of the latter has been made possible by recording the claudication index before and during experimental arterial occlusion in the affected limb. In cases in which the difference between these indices is very small, the prognosis has been regularly bad. In

very severe cases there may be no difference at all. A big difference, which means a considerably higher index with a free circulation, as compared with that during experimental arterial occlusion, is proof of a good vascular reserve and usually indicates a better prognosis. As a rule, patients give a history of intermittent claudication in one leg only. Despite this, the underlying pathologic condition is, in most cases, as judged by the diminished claudication index, bilateral. The condition of the "unaffected" leg can thus be assessed.

SUMMARY

A standardized ergographic method, by means of which a claudication index may be ascertained, has been described. This is related to the blood flow through active muscle only. In 97 per cent of the normal subjects the indices were above 50, and, in 95 per cent of the abnormal, below 40. It appears, therefore, that the circulation in a limb in which the claudication index is less than 40 is deficient, provided the muscle itself and its nerve supply are normal. Thus the degree of impairment of the circulation in the legs can be estimated. Definite relations between the degree of intermittent claudication and the claudication indices have been established. The status of the circulation to muscles can be gauged by comparing the claudication index after experimental, complete, arterial occlusion with that obtained when the arterial circulation has not been mechanically interfered with. The difference between these indices can be taken as an expression of the vascular reserve.

I wish to express my gratitude to Professor C. F. M. Saint for his interest in this work. It is with pleasure that I record my thanks to the members of the Honorary Staff of the Groote Schuur Hospital for kindly permitting me to study patients who were admitted under their care. To the many students and staff members who willingly served as subjects I extend my thanks.

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STUDIES ON THE THIRD HEART SOUND

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IN A PREVIOUS paper[1] the suggestion was made that the third heart sound might originate in the chest wall, rather than in the heart itself. The following observations served as a basis for this suggestion. (a) A third sound had apparently never been recorded from the exposed heart of experimental animals; (b) it had not been recorded from the esophagus of man even though it could easily be recorded from the precordium of the same subject;[2] (c) the natural period of the human thoracic wall was of the same low frequency as the normal third sound; and (d) records of the apex beat indicate that an impact is imparted to the chest wall at the moment of the third heart sound.

Because it seemed desirable to gather more evidence for or against such a theory, the present study of registration of sounds from the exposed heart of experimental animals was undertaken.

METHODS

Dogs, weighing 6 to 8 kilograms, were anesthetized with morphine and intravenous sodium pentobarbital. Under artificial respiration the heart was exposed by resection of the left ribs, and sounds were recorded* directly from the surface of the left ventricle. Simultaneous records of the venous pulse, apex beat, or electrocardiogram were made. The heart sounds were transmitted to the recording apparatus by means of (a) a light wooden lever, one end of which was sewed to the myocardium and the other was cemented to a tight rubber membrane covering the open end of a large bell, (b) flexible rubber tubing sewed to the myocardium and connected to the rigidly supported microphone, the length of tubing being sufficient to absorb the movements of the heart, (c) a small shallow bell, 2.5 cm. in diameter, introduced through an opening in the parietal pericardium and held in place by sutures through the edges of the pericardium, and (d) a glass cardiometer enclosing the heart.

RESULTS

Experiments were done on five dogs. Fig. 1*A* shows the sounds recorded directly from the left ventricle using a rubber tube with an

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*All recording was done with the Stetho-Cardiette manufactured by the Sanborn Company, Cambridge, Massachusetts.

internal diameter of 3 mm. and a wall thickness of 2 mm. as a receiver; *B* shows the sounds recorded from the same animal through a tube of 6 mm. internal diameter and wall thickness of 2 mm. Record *C*, also made from the same animal, shows the sounds recorded with a bell 2.5 cm. in diameter, and simultaneous electrocardiogram. The relative sensitivity, or degree of amplification, for the records in Fig. 1 are *A* 11.5, *B* 5.5, and *C* 1. It appears that, despite increasing sensitivity, sounds are more and more attenuated by decreasing the size of the receiver applied to the heart.

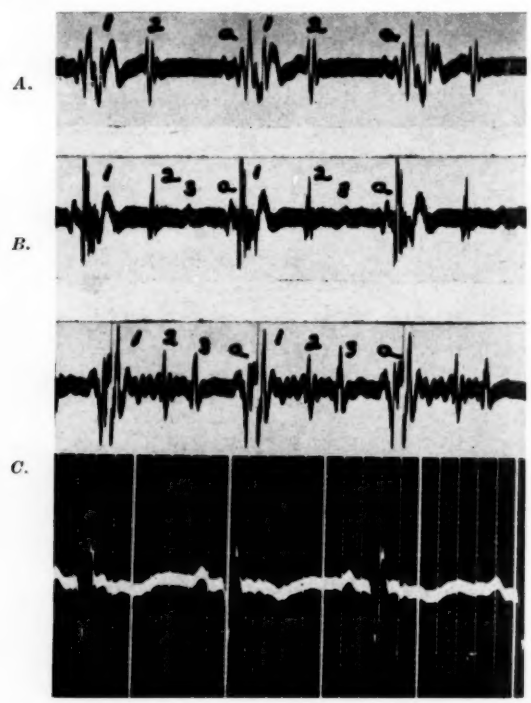


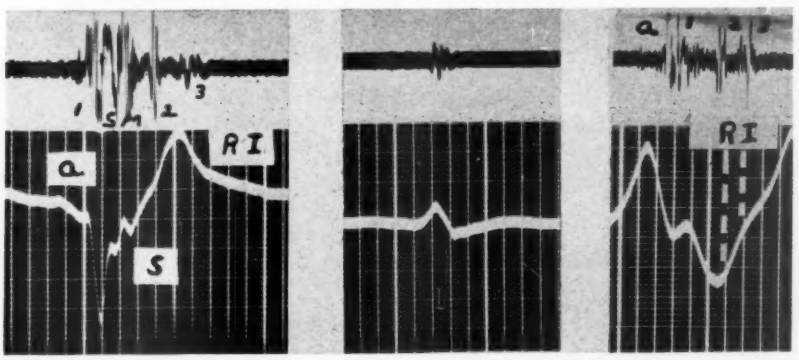
Fig. 1.—Sounds recorded directly from the surface of a dog's heart with simultaneous electrocardiogram. *A* is a record obtained when rubber tubing of small internal diameter (2 mm.) was used. Record *B* was obtained with larger sized tubing (internal diameter 6 mm.), while *C* was obtained with a shallow bell 2.5 cm. in diameter. The degrees of amplification used for *A*, *B*, and *C* were 11.5, 5.5, and 1, respectively. Note the absence of the third sound in record *A* and the progressive prominence of the third sound in records *B* and *C* as the size of the receiver is increased.

Despite very high degrees of amplification a third heart sound could never be distinguished in records made with a wooden lever or small rubber tubing sewed to the ventricle. Small vibrations at the expected moment of the third sound could usually be discerned when the larger bore tubing was used as a receiver and were prominent when recorded with the bell.

With the bell held in place only by sutures through the pericardium, uniform contact with the heart throughout the cycle could not be as-

sumed with confidence. The question naturally arose whether the impact of the beating heart against the bell might give rise to vibrations which need not be present normally.

Accordingly the following tests were made after the heart had been stopped by asphyxia. Mechanical impacts and sound vibrations were recorded from the ventricle during such manipulation of the heart as to cause it to strike the receiving bell gently. Both recording instruments were adjusted to the sensitivity which was previously used in recording from the beating heart, and records showing a mechanical impact of the same magnitude as the normal protodiastolic wave seen in the apex cardiogram were selected for study. It was found that a sound was thereby produced which was identical with the third sound in amplitude, frequency, and duration (Fig. 2*A* and *B*). The force applied to the heart to produce such an effect was so small as to preclude any interpretation other than that the sound was produced by vibration of the ventricular wall.



A. *B.* *C.*

Fig. 2.—*A* shows the heart sounds and apex impulse recorded from the exposed heart of a dog after the onset of asphyxia. The heart sounds are labeled *1*, *2*, and *3*. There is a systolic murmur which was not present in records obtained before asphyxia. In the apex cardiogram the auricular wave is labeled *a*; ventricular systole, *S*; and the rapid inflow phase, *RI*. The asphyxial record was chosen in order to make the vibration of the ventricular wall comparable with the record obtained in the quiescent heart at the end of asphyxia (*B*). *B* shows the sound (upper) and mechanical impact (lower) produced by a gentle impact of the quiescent, asphyxiated heart against the bell in the same animal from which record *A* was obtained. The sensitivities of both the sound and mechanical recorders were the same for both *A* and *B*. It will be seen that the mechanical impact is very nearly the same as the rapid inflow curve (*RI*) in *A* and that the sound produced is identical with the third heart sound. Record *C*, obtained from another animal, shows the heart sounds and ventricular volume curve, both recorded from a cardiometer in which impacts against a receiver are eliminated, and thus any possible unnatural vibrations arising from such a source are excluded. It is evident that the third heart sound continues to be present under these circumstances and occurs toward the end of the rapid filling phase (*RI*), indicated on the volume curve by the broken lines.

It was because of this observation that records were made with a cardiometer with the intent of eliminating any such unnatural vibrations. Since undoubted third sounds appeared in records obtained from the glass oncometer surrounding the heart, where impacts were certainly minimal, if not entirely eliminated, it seems clear that the sound arises in the heart (Fig. 2*C*).

When third sounds were not spontaneously present, they could always be produced by rapid intravenous infusion of saline, thereby increasing the velocity of flow during the rapid inflow phase, or by asphyxia.

DISCUSSION

The transmission and graphic registration of sound is a complex subject, influenced primarily by the relationship of the natural frequency and sensitivity of the apparatus to the frequency and intensity of the sound to be recorded. Due to resonating properties of recording systems, the registration of a low-pitched sound, such as the third heart sound, is best accomplished by a system of low natural frequency. Introduction into such a system of a transmitter made of stiff, insensitive material with a high natural frequency, such as wood or bamboo, will greatly attenuate low-pitched vibrations and will materially decrease the sensitivity for other frequencies as well.

Furthermore the receptor portion of the recording system serves as a cumulator of sound vibrations. Since the total energy emitted from a vibrating source is radiated in all directions, it is evident that the smaller the receiver, the less will be the proportion registered. It is admitted that this factor is probably of less importance than is the effect of introducing a relatively insensitive "high frequency" component into the system. The property of the receiver as a cumulator of sound cannot, however, be neglected.

With these principles in mind one finds little cause for wonder that a method involving the use of a relatively small solid receiver made of wood should prove inadequate for the registration of the low-frequency, low-intensity third heart sound. Unfortunately this method has been adopted frequently for the study of heart sounds recorded directly from the heart[3, 4] and is responsible for the erroneous deduction that, since the third heart sound was not recorded, it was not present in the heart.

Having accounted for the absence of third heart sounds previously recorded from the exposed heart of experimental animals, one can speculate as to the probable explanation for their absence in esophageal records. It was discovered in the present study that transmission by small bore tubing resulted in considerable attenuation of the first and second sounds while the third sound was eliminated entirely. In part this attenuation is due to the small size of the receiver as a cumulator of sound. Of greater importance, however, is the behavior of open receivers when they are applied to soft tissue.

Rappaport and Sprague[5] have pointed out that under such circumstances the tissue in contact with the receiver becomes, in fact, a diaphragm. When the receiver is large, this diaphragm has a low natural frequency and high sensitivity. Progressive decrease in the size of the

receiver results in increasing natural frequency and diminishing sensitivity of the diaphragm with consequent attenuation of all sounds but with especially adverse effects on low-frequency vibrations.

Since, of necessity, esophageal records are obtained with small bore tubing, and since the esophagus will be collapsed around the lower end of the tube, it seems probable that the same diaphragm effect may play a role here. Furthermore the degree of frictional loss in small tubing of excessive length may be considerable and will serve to further attenuate the sounds. Other factors, as yet incompletely evaluated, will perhaps further account for the absence of third heart sounds in esophageal records.

The high proportion of third heart sounds recorded from the precordium of normal subjects by Orias and Braun-Menendez[6] can be assigned to a method of registration which is particularly adapted to the reproduction of low-frequency, low-intensity sounds. Not only is the membrane which they used in the recording Frank capsule very loose (therefore of high sensitivity and low natural period), but also the chest piece employed was of very large size. This large receiver was designed to serve as a better cumulator of sound, which it does, but it also provides for a sensitive, low-frequency "skin diaphragm" when applied to the chest wall.

Although the exact mechanism of the production of the third sound is not known, there is general agreement that it is somehow produced by rapid filling of the ventricle during early diastole. Gibson[7] and Hirschfelder[8] were the first to suggest that the sound was created by vibration of the auriculoventricular valves toward the end of the rapid filling phase. This view has recently been supported by Lewis and Dock.[9] On the other hand, the South American school[6] vigorously supports the theory, first proposed by Ohm,[10] that the sound is produced by vibration of the ventricular walls. In rejecting the latter theory, Lewis and Dock wrote, "The rubbery mass of heart muscle, which from a physical standpoint seems an ideal sound deadening substance, apparently gives off no audible vibrations. Its contraction, or filling, or even its forceful impact against the chest wall contributes nothing to the heart sounds. The fact that audible vibrations can be obtained from thin strips of muscle isolated from the ventricle is of no significance, for it is easy to produce sounds with a thin rubber band but almost impossible with a rubber ball as thick walled as the heart."

This stand is untenable in view of the demonstration that the ventricular wall does give off vibrations in the audible range (Fig. 2*B*). It would be rash to claim that the present observations finally establish the cause of the third heart sound as due to vibration of the ventricular wall, but they do demonstrate that vibration of the ventricular wall can produce a sound comparable in every way with the normal third sound.

SUMMARY

Heart sounds were recorded directly from the surface of the dog's heart in order to confirm or refute a previously made suggestion that the third heart sound might have its origin in the chest wall. Third sounds could readily be recorded when large, open receivers were used but not with small open receivers or when the traditional light wooden lever was used.

The physical laws bearing on the explanation for the absence of third sounds in previous records from the exposed heart of animals and from the esophagus of man have been briefly considered.

Evidence was presented to show that vibration of the ventricular wall, produced in the quiescent heart by a very feeble impact, gave rise to a sound very like the normal third sound in frequency, amplitude, and duration.

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THERAPEUTIC PERICARDITIS BY INTRAPERICARDIAL INJECTION IN CHRONIC CORONARY INSUFFICIENCY

A Preliminary Report

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THE production of a sterile inflammatory reaction between the epicardium and pericardium by the direct introduction of an irritant substance into the pericardial sac has been demonstrated by many investigators. As a result of the adhesive pericarditis, a collateral vascular bed may be enhanced to such an extent that beneficial clinical effects have been observed in the treatment of coronary artery sclerosis with chronic coronary insufficiency.

The coronary arteries are normally physiologic end arteries but have anatomic facultative intercommunications. Atherosclerotic changes occur at birth and may gradually progress until death without impairing the circulation to the myocardium.[1] This latter might be termed physiologic coronary artery disease. Here the intimal thickening is uniform and concentric with no encroachment on the lumen. But when the process becomes eccentric, definite narrowing with diminution of blood flow occurs and pathologic coronary artery disease is present. Paradoxically, the development of a functioning collateral circulation is dependent on the extent of the disease process in the arteries. Rupture of the capillaries of the vascularized intima produces intramural hemorrhage and complete occlusion of the vessel. This obstruction to normal arterial flow through the coronary vessels is the actual stimulus to anastomotic development. If these occlusive processes are gradual, differential pressure gradients dilate previously impervious arterioles to effect an adequate collateral circulation to a potentially ischemic myocardium.[2] Experimentally Burchell[3] demonstrated that it was possible to occlude the three main coronary branches in the dog without the production of an infarct or even demonstrable cardiac disability. In the human being Blumgart and his collaborators[4] pointed out that, even though all three main coronary arteries were occluded, no infarctions resulted because of the development of a compensatory anastomotic circulation.

In many instances revascularization of the ischemic heart by these spontaneous processes does not suffice; therefore surgical measures have been used. Vascular channels in pericardial adhesions have been demonstrated by many studies. Moritz, Hudson, and Orgain[5] have shown experimentally in human hearts with adhesive pericarditis that india ink injected into the coronary arteries could be traced into the

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pericardium, chest wall, and diaphragm. Thus the artificial production of a sterile adhesive pericarditis might be conducive to the development of a functioning collateral circulation to the heart. Parietal grafts to the abraded myocardium with the production of an adhesive pericarditis have been employed. Beck[6, 7] used a pedicled graft of the pectoralis major and burr or powdered bone meal, while O'Shaughnessy[8] performed a cardio-omentopexy and for his irritant used aleuronat. Thompson[9] did a pericardiotomy and employed talc (anhydrous magnesium silicate) to produce the adhesive pericarditis without parietal grafts.

The beneficial clinical results reported by the above-mentioned investigators have been encouraging, but the surgical procedures employed have been delicate and tedious with no little risk to a subject with an incompetent heart. If one could produce an adhesive pericarditis without pericardiotomy, much surgical trauma could be avoided. Heinbecker and Barton[10] were able to bring about an adhesive pericarditis experimentally in dogs by injecting a sclerosing mixture of gelatin, aleuronat, starch, glycerine, and water into the pericardial sac and, as a result of this procedure, demonstrated an adequate collateral circulation to areas of myocardium rendered ischemic by tying of branches of the coronary arteries. Beck[11] has mentioned the possible use of other injectable substances as sodium morrhuate. But no cases have been reported in man. It is the purpose of this paper to report two cases of pericarditis produced by the injection of an irritating substance directly into the pericardial sac of man without exposing the heart.

TECHNIQUE

The site selected for the pericardial puncture is the fifth left interspace just outside the apex impulse. Under aseptic conditions this area is infiltrated with 1 per cent novocaine solution. A long needle of large bore, attached to a 10 c.c. syringe filled with air, is inserted cautiously and directed medially, slightly posteriorly and cephalad. When a faint tugging sensation is perceived synchronous with the pulsations of the heart, the needle is very slightly withdrawn and 10 c.c. of air is injected under the fluoroscope. The appearance of a slight pneumocardium signifies a proper introduction of the needle into the pericardial sac, and now the sclerosing solution is injected. This consists of 18 c.c. of 5 per cent sodium morrhuate (Searle) plus 2 c.c. of iodochlor (Searle). The radiopaque character of the latter is so pronounced that it may be diluted several times and still retain its efficacy for roentgenographic studies. Thus should the needle slip outside the pericardial sac, while changing syringes, the heavier, opaque, nonirritating iodochlor would first be seen running into the pulmonary field. Following completion of the injection, the failure to visualize the opaque substance in the pulmonary fields on further roentgenographic studies is obvious evidence that it has been properly introduced into the pericardial sac.

CASE REPORTS

CASE 1.—E. V., a white male, aged 74 years, was admitted to the Kingston Hospital Nov. 6, 1941, because of an episode of recurrent congestive heart failure. He first complained of exertional dyspnea in the fall of 1936 and shortly thereafter noted edema of the lower extremities accompanied by asthenia and occasional orthopnea. In the summer of 1937, he was confined to bed for twenty-eight days because of orthopnea, cough, marked edema of the lower extremities and slight ascites. Under a therapeutic regime of bed rest, xanthines, and small doses of digitalis, a clinical improvement was noted. Subsequently, at intervals of four to six months, he suffered with similar attacks of congestive heart failure. However, dyspnea on exertion accompanied by precordial distress has always been present.

Physical examination revealed a well-preserved, orthopneic, acyanotic white male. On examination of the fundi oculorum there was observed marked tortuosity and thickening of the retinal arteries but no hemorrhages or atrophic areas and the disc margins were clear. There was slight distention of the veins in the neck. Numerous crackling râles were heard at the bases of both lungs. The heart was moderately enlarged. A_2 was greater than P_2, and except for an inconstant, very slight, soft, systolic, apical murmur no adventitious sounds were heard over the precordium. The blood pressure was 118/84 to 118/80, and the pulse rate was 78 with regular rhythm. Ascites and a marked hard edema of the lower extremities were present. A teleroentgenogram showed marked general enlargement of the cardiac silhouette. There was broadening of the shadow over the area of the great vessels with some hilar thickening and accentuation of the lung markings. Except for obliteration of the left diaphragm and costophrenic angle the periphery of both lung fields was clear. An electrocardiogram revealed occasional premature ventricular systoles, left axis deviation, and inverted T waves in Lead I and the precordial lead (IVF). Chemical examination of the blood and urine revealed nothing significant. Microscopic examination of the urine revealed a moderate number of pus cells. There were 74 per cent of hemoglobin in the blood (15.6 Gm. equals 100 per cent), 4,260,000 erythrocytes per cubic millimeter, and 7,400 leucocytes per cubic millimeter of which 72 per cent were polymorphonuclear neutrophiles. Serologic tests revealed no evidence of syphilis.

A diagnosis was made of arteriosclerotic heart disease with coronary arteriosclerosis and chronic coronary insufficiency, cardiac hypertrophy with diffuse myocardial fibrosis, and congestive heart failure. Therapy consisted only of bed rest and small doses of diuretin (10 gr. twice daily for five days). On Nov. 8, 1941, an unsuccessful attempt to introduce 5 per cent sodium morrhuate into the pericardial sac produced no ill effects. This was not done with the radiopaque substance under the fluoroscope, and apparently the solution was injected into the left pulmonary field. The temperature rose to 101.2° F. for only twenty-four hours, and roentgenograms revealed no pulmonary changes. Adventitious sounds were not heard over the precordium, and the patient made no complaints.

On Nov. 11, 1941, a pericardial injection was successfully performed by the above-described technique. The patient complained only of slight temporary pain in the left side of the chest and the left arm. Within a few hours the temperature rose to 103.2° F. and was accompanied by a leucocytosis of 14,800 with 89 per cent of polymorphonuclear leucocytes. A faint, localized pericardial friction rub over the apical area was not heard until eighteen hours later. This soon increased in intensity and distribution and persisted until eight days later at which time both the leucocyte count and temperature had receded to normal levels. The blood pressure and pulse rate did not vary appreciably. On November 16, the peripheral edema, ascites, and dyspnea were no longer present, and surprisingly enough immediately after the operation the patient enjoyed bathroom privileges, smoked cigars, and felt entirely comfortable. Complaints were

referred only to the genitourinary system because of prostatic disease. Roentgenographic studies revealed a clearing of the disturbance at the base of the left lung. Electrocardiograms did not differ significantly from the one reported until early in the third week when T wave negatively appeared in Lead II and became more pronounced in Leads I and IVF.

CASE 2.—E. B., a white female, aged 74 years, was admitted to the Kingston Hospital on Nov. 21, 1941, because of congestive heart failure. The patient had suffered from recurrent bouts of congestive heart failure for the past three years but first noted exertional dyspnea and precordial distress about five years ago. Her symptoms were usually alleviated by a combination of xanthines and very small doses of digitalis. However, the last attack had not responded to this therapy, and hospitalization was advised.

Physical examination revealed a very dyspneic, apprehensive woman. There was slight cyanosis of the lips, ears, and fingers, and the veins of the neck were markedly distended. Examination of the fundi oculorum revealed no significant retinopathy. At the bases of the lungs there was slight impaired resonance with many crackling râles. The heart was moderately enlarged, but no adventitious sounds were heard on auscultation. A_2 was greater than P_2, and the blood pressure was 150/82 to 150/80. A markedly enlarged, tender liver was associated with a moderate ascites. The lower abdominal wall and lower extremities were edematous; the edema was of a soft, pitting variety.

Electrocardiographic studies demonstrated nodal rhythm with an occasional premature ventricular systole and low voltage in all leads (0.2 to 0.3 millivolts). The venous pressure in the right arm was 24.5 cm. of water. A roentgenogram of the chest revealed some hilar thickening with accentuation of lung markings, slight bronchial infiltration, and some haziness over both bases. The cardiac shadow was enlarged. Chemical analyses of the blood were not significant. Serologic tests for syphilis were negative. The erythrocytes numbered 4,960,000 per cubic millimeter of blood with 85 per cent of hemoglobin (15.6 Gm. equals 100 per cent), and the leucocytes numbered 5,950 per cubic millimeter of which 52 per cent were polymorphonuclear neutrophiles. Examination of the urine revealed a slight trace of albumin, 5 to 8 pus cells, and a few fine and coarse granular casts per low-power field.

A diagnosis was made of arteriosclerotic heart disease with coronary artery sclerosis and chronic coronary insufficiency, cardiac hypertrophy with diffuse myocardial fibrosis, and congestive heart failure. Therapy consisted only of bed rest and barbiturate sedation.

On November 23, a successful injection into the precordial sac was performed. Within twenty minutes a very loud, harsh pericardial rub was heard over the entire precordium. Curiously enough, the rub completely disappeared at the end of one hour. Eighteen hours later there was a mild febrile reaction (100.8° F.) accompanied by a slight leucocytosis which persisted for four days and was associated with a slight pericardial quality to the heart sounds. At no time did the early electrocardiograms reveal elevation of the S-T junction but rather absent positive deflection in the precordial lead (IVF) together with a diphasic T wave. The blood pressure and pulse rate did not vary significantly. The only untoward symptom was vomiting. This appeared shortly after the injection and continued at intervals for five hours, but was believed to be due to an error in diet plus sensitivity to morphine, which had been administered preoperatively. The patient's subsequent clinical improvement was remarkable. Five days after this procedure a slight ascites was the only residual manifestation of her severe congestive heart failure. The patient stated she breathed more easily and felt generally better. She was discharged twelve days after her treatment at which time an electrocardiogram showed T_1 and T_2 to be inverted as was the T wave in the precordial lead (IVF).

COMMENT

In 1932, Hudson, Moritz, and Wearn[12] demonstrated the rich potential extracardiac coronary circulation to the human heart, and a contemporary publication mentioned that this extrinsic collateral circulation was augmented by pericardial adhesions. In addition Mautz and Beck[13] reported that the intercoronary collateral circulation was enhanced by these adhesions. Subsequent experimental and clinical observations have shown the efficacy of a collateral vascular bed to the myocardium brought about by an adhesive pericarditis. Experimentally in rabbits we have produced an adhesive pericarditis by exposing the pericardial sac and injecting a solution of 5 per cent sodium morrhuate plus a small amount of iodochlor with no deleterious effects.

A similar solution injected without exposure into the pericardial cavity of two patients suffering with arteriosclerotic heart disease and chronic coronary insufficiency has produced a clinical pericarditis without interference of the heart action. The clinical manifestations of pericarditis were fever, leucocytosis, and pericardial friction rub, and, although S-T segment alterations usually observed in acute pericarditis were absent, later electrocardiograms showed T-wave inversions suggestive of a healing stage in acute pericarditis. Since the work of Burchell and his collaborators[14] seems to indicate that such changes are caused by a subepicardial myocarditis, we may accept these T-wave alterations as evidence that the epicardial barrier between intercoronary and extracoronary circulation has been removed. The early clinical improvement observed might be caused by the rapid opening of intercoronary communications.[15] However, the permanency of the beneficial effects of this attempted revascularization of the myocardium will also be dependent on the extracardiac anastomoses. This is doubted by some investigators[3] who have been unable to find supportive evidence that vascularized tissue grafts play a useful function in the re-establishment of coronary circulation following experimental occlusion of the coronary arteries. Certainly further clinical observation and histologic studies are necessary in my limited number of cases. Appreciating the paucity of material at hand, I suggest this method of producing a sterile, adhesive pericarditis in the treatment of myocardial ischemia in man in the hope that others may further investigate its possibilities.

CONCLUSION

A pericarditis, the result of injecting an irritating substance into the pericardial sac, has been employed in the treatment of two cases of chronic coronary insufficiency with apparent beneficial results.

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APICAL DIASTOLIC MURMURS WITHOUT MITRAL STENOSIS

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THE occurrence of a rumbling diastolic murmur at the apex, exclusive of the Austin Flint murmur, unaccompanied by organic mitral stenosis, has long been known. As early as 1894 Fisher[1] published five such cases. The following year Phear[2] reported two cases and collected nineteen others from the literature. From the writings of Hirschfelder,[3] Flint[4] and Cabot[5] it is evident that they were cognizant that apical diastolic murmurs could occur in enlarged hearts without mitral stenosis. In 1923, Wood and White[6] reviewed twenty necropsy records of patients with marked cardiac hypertrophy with normal valves. Four of these had diastolic murmurs at the apex. In 1929, Bach and Keith[7] presented a similar case. Sheldon,[8] McKee,[9] Schlesinger[10] and Taussig[11] pointed to the presence of a diastolic murmur in the early stages of rheumatic disease before the appearance of mitral stenosis. In 1933, Gunewardene[12] pointed out that a presystolic or diastolic murmur with clinically marked cardiac dilatation often occurs in children with ankylostoma infection. With treatment the heart returned to normal size and the murmurs disappeared. Bland, White, and Jones[13] in 1935 reported a series of 100 patients dying with rheumatic heart disease. Clinical mitral stenosis was diagnosed in sixty-eight cases while anatomic stenosis was present in only twenty-three. This was re-emphasized by the authors in 1936.[14] Yet Thompson and Levine[15] from a clinical and pathologic correlation report a high degree of accuracy in the diagnosis of mitral stenosis, either when it occurs alone or when it is associated with other valvular lesions.

We have studied clinically five patients with diastolic murmurs at the apex who showed no mitral stenosis pathologically. In view of the general belief that the mild or low rumbling diastolic murmur at the cardiac apex (in the absence of aortic regurgitation) signifies organic mitral stenosis, we present these cases.

CASE REPORTS

CASE 1.—T. M., a 15-year-old white female, entered Michael Reese Hospital on March 4, 1937. She had had frequent attacks of tonsillitis, and one year before entry she had her first attack of polyarthritis, at which time rheumatic heart disease was diagnosed. Because of persistent fever, orthopnea, and precordial pain, she was referred to the hospital. The heart was enlarged and P_2 was accentuated. All

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of the medical staff agreed at various times during her stay that there were systolic and diastolic murmurs at the apex, some calling the latter mid-diastolic and others presystolic. Likewise all agreed that there was a diastolic thrill at the apex (some calling it presystolic). The x-ray and fluoroscopic examination confirmed the presence of an enlarged heart and also showed the left auricle appearing within the shadow of the right auricle. The liver edge was palpable, 1 fingerbreadth below the costal margin. She improved, was sent home after two months, and was followed in the outpatient clinic for a few months. She was referred back to the hospital on Aug. 7, 1937, because of dyspnea and orthopnea. All during this period the heart findings were the same as above. On this admission, in addition to the apical findings, one observer heard at the third and fourth left interspace, a soft diastolic murmur which subsequently disappeared. The blood pressure at this time was 108/66 mm. Hg. Subsequent blood pressures ranged from 122 to 100 systolic and 94 to 64 diastolic. She improved after a six months' stay, was home for five months, and re-entered in severe heart failure. Again all observers agreed that there was a double murmur at the apex with a diastolic thrill. The blood pressure varied from 126/94 to 92/60. After seven more months the patient died in heart failure.

Post-Mortem Examination of the Heart.—The heart was markedly enlarged to the right and left; it weighed 400 Gm. There were firm adhesions between the pericardium and epicardium, in addition to some fine easily separated strands. All chambers of the heart were dilated. The endocardium of the left auricle adjacent to the inferior leaflet presented multiple coarse corrugations and wrinklings. The mitral orifice measured 10.4 cm. in circumference. The line of closure of the leaflets of the mitral valve showed minimal to moderate thickening with a row of fine verrucae. The corresponding chordae tendinae were moderately thickened, in a few spots fused, and somewhat shortened. The circumference of the aortic orifice measured 7 cm. The cusps of the aortic valve were slightly thickened, and shortened, and minimally adherent at the commissures. The circumferences of the tricuspid and pulmonic valves measured 11 and 8 cm., respectively. The corresponding valves presented no gross changes. On section the myocardium was greyish red and parboiled in appearance. Microscopically the myocardium revealed swollen and poorly stained muscle fibers. There was a diffuse, loose network of fine fibrillar connective tissue separating small groups of muscle fibers. Many areas presented a perivascular, markedly eosinophilic, fibrillar substance with particles of swollen collagen and a moderate distribution of lymphocytes, fibroblasts, and plasma cells. An occasional Aschoff body was noted. The diagnosis was (1) old endocarditis of the mitral and aortic valves with insufficiency of their orifices (aortic minimal, mitral moderate), (2) old mural endocarditis, (3) acute verrucous endocarditis of the mitral valves, (4) acute and old rheumatic myocarditis, (5) old pericarditis, (6) chronic passive hyperemia of the lungs, liver, spleen, kidneys, and gastrointestinal tract, (7) fatty degeneration of the liver, (8) fibrosis of the spleen, (9) ascites, and (10) peripheral edema.

Case 2.—J. K., a female child, was first seen on Dec. 27, 1931, at the age of 5.5 years and was followed for a period of six years. She had scarlet fever at the age of 3 years. Her first entry into Sarah Morris Hospital was because of chorea, and during her course she had multiple such attacks. On her first admission a soft systolic murmur was heard at the apex with an accentuated first sound. The heart was not enlarged. On her second and third admissions at the age of 8, definite harsh systolic and diastolic murmurs were heard at the apex, coupled with a mitral configuration of the heart on x-ray examination, and a right axis shift in the electrocardiogram. She was not in failure, but periodically continued to run a febrile course. On her readmission at the age of 11, the diastolic murmur was questionable, although the other findings were the same. On her final admission she was in

heart failure. Systolic and diastolic murmurs were again heard at the apex, and electrocardiogram and x-ray examination were as previously. Hoarseness developed which was interpreted as being due to left auricular pressure on the recurrent laryngeal nerve. The patient gradually became worse and died in marked congestive failure.

Post-Mortem Examination of the Heart.—The heart was markedly enlarged to the right and left and weighed 300 Gm. On the epicardium covering the left base anteriorly there was an irregular, white streaked plaque. The tricuspid orifice measured 12 cm. in circumference. The valve leaflets presented numerous firm, pinkish-grey excrescences. The mitral orifice measured 13 cm. in circumference, and similar excrescences were present on the line of closure of the inferior leaflet. The edges of both leaflets of this valve had a somewhat scalloped appearance. The aortic and pulmonic orifices measured 7 and 8 cm. in circumference, respectively, and the corresponding valves were normal. All cardiac chambers were markedly dilated. The myocardium was markedly flabby, pale, reddish brown, and distinctly parboiled in appearance. Microscopic examination revealed a moderate perivascular fibrosis throughout the myocardium. In some areas there were accumulations of lymphocytes and endothelial leucocytes. The muscle fibers were larger than normal, and the intercalated discs were very prominent. No Aschoff bodies were noted in the myocardium. The endocardium revealed occasional foci of lymphocytes and fibroblastic cells. The diagnosis was (1) chronic myocarditis, (2) old endocarditis of the mitral valve with acute verrucous endocarditis of the tricuspid and mitral valves, (3) moderate hypertrophy and marked dilatation of the heart, most marked in the right ventricle, (4) chronic peri- and endarteritis of the smaller branches of the pulmonary artery, with organized and organizing thrombi and pulmonary infarcts, (5) chronic passive hyperemia of the lungs, liver, and spleen, (6) left hydrothorax, ascites, and peripheral edema, (7) recent and organizing bronchopneumonia, (8) subacute splenic hyperplasia, and (9) cloudy swelling of the kidneys.

CASE 3.—E. L., a 25-year-old white female, entered Michael Reese Hospital on July 15, 1921, in the puerperium of a complicated labor, complaining of chills, fever, and marked weakness. She gave a previous history of scarlet fever. Physical examination at this time revealed râles in the lungs with high fever and no enlargement of the heart. A soft, blowing nontransmitted, systolic murmur was heard at the apex. The patient's course was septic for four months during which time the heart size gradually increased. With the disappearance of the sepsis the heart remained enlarged. The patient was discharged on Dec. 19, 1921, five months after entry. A diagnosis of post-infectious myocarditis was made. Seven years later the patient was seen in heart failure, with marked cardiac enlargement and auricular fibrillation. No definite murmurs were heard at this time. The blood pressure was 124/80. A half year later a pulsating, inguinal mass was discovered, and a questionable diastolic murmur at the apex was heard. A diagnosis of arteriovenous aneurysm was now made. Four years later the patient was again seen in right heart failure and auricular fibrillation. This time various observers described a loud, rough, long drawn out, crescendo, presystolic murmur, or diastolic murmur at the apex. A diagnosis was now made of rheumatic heart disease with mitral stenosis and insufficiency. In two subsequent bouts of heart failure two and three years later no distinct murmurs could be heard because of the weak and irregular heart action. The blood pressures on the two admissions were 110/70 and 100/70, respectively. In her last attack, however, six months later, a presystolic murmur was again heard. The patient died in right heart failure on March 19, 1936. The final diagnosis was arteriovenous aneurysm, and mitral insufficiency and stenosis.

Post-Mortem Examination.—Two arteriovenous aneurysms were found involving the right iliac and right external pudendal veins and arteries, respectively. The

heart was tremendously enlarged and filled three-fourths of the chest cavity. It weighed 425 Gm. The enlargement was due mostly to dilatation of the right auricle and ventricle, although the left auricle and ventricle were also moderately dilated. The right and left ventricular walls measured 0.3 to 0.4 cm. and 1 cm., respectively. The circumference of the mitral valve was 10 cm. The line of closure of the leaflets was somewhat thickened, and the chordae were slightly shortened. Several small verrucae were present on the inferior leaflet. The tricuspid orifice was markedly dilated, but its valve showed no change. The orifices and leaflets of the aortic and pulmonic valves were normal. Several small areas of fine granularity were present on the pericardium. The endocardium showed no gross changes. Histologically the fibers of the myocardium were swollen and their cytoplasm was pale stained with obscure striations. The fibers of the right ventricle were somewhat enlarged. The perivascular connective tissue was moderately increased in amount and occasionally infiltrated with round cells. The walls of the arteries were slightly thickened and hyalinized. The epicardium was thickened and edematous with many round cells embedded in fibrin. The diagnosis was (1) marked hypertrophy and dilatation of the right ventricle and auricle, (2) marked dilatation of the tricuspid orifice with insufficiency of the valve, (3) acute verrucous endocarditis superimposed on a healed endocarditis of the mitral valve with questionable insufficiency, (4) acute serofibrinous pericarditis, (5) arteriovenous aneurysms involving the right iliac and right external pudendal veins and arteries, (6) marked chronic passive hyperemia of the liver, spleen, and kidneys, and (7) bilateral hydrothorax, ascites, and peripheral edema.

CASE 4.—P. D., a 21-year-old white male, entered Michael Reese Hospital on Feb. 17, 1933, with a history of progressive weakness, dyspnea, and mild precordial pain of four months' duration. He had never suffered from rheumatism, scarlet fever, chorea, or tonsillitis. Physical examination at time of admission revealed enlargement of the heart to the right and left on percussion. Apical murmurs were described by some as presystolic and systolic, and by others as systolic and rumbling diastolic. A soft diastolic murmur was heard over the aortic area and in the third and fourth left interspace by some, and not heard by others. The liver was just palpable, while the spleen was distinctly palpable. The arterial blood pressure on admission was 102/40. The temperature was 100° F., and the pulse rate was 104. A diagnosis of rheumatic heart disease with mitral stenosis and insufficiency and possible aortic insufficiency was entertained, with subacute bacterial endocarditis to be ruled out. The patient was in the hospital for six weeks. A rumbling apical diastolic murmur continued to be heard, while the diastolic pressure rose to 60 mm. The temperature fell to normal; the patient improved, was up and about, and was discharged on April 3, 1933, on a regime of restricted activities and on digitalis. He was readmitted to the hospital on April 13, 1934, with sudden sharp severe pain beneath the left lowermost ribs, accompanied by nausea, vomiting, and shortness of breath. Physical examination revealed enlargement of the heart with auricular fibrillation. This time, however, no apical murmurs were heard. A systolic and diastolic thrill, or murmur, or both were heard and felt over the pulmonic area by various observers. The liver was now distinctly palpable while the spleen was not. The arterial blood pressure was 100/70. The patient died after four days in congestive heart failure.

Post-Mortem Examination of the Heart.—The heart was markedly enlarged to the right and left and weighed 550 Gm. All chambers were dilated, especially the left ventricle. The valvular apparatus presented no abnormality. The myocardium was soft and flabby throughout. On section its normal architecture was obscured, its cut surface being shaggy, granular with numerous minute, irregularly demarcated, pinkish-grey areas and streaks. Recent mural thrombi were present in the left

ventricle and the right auricle. The pericardium showed no changes. Microscopic examination revealed a diffuse moderate new formation of connective tissue containing a moderate number of lymphocytes and endothelial leucocytes. In addition there was a distinct perivascular infiltration of similar cells. Only an occasional section presented a few larger cells with distinct basophilic cytoplasm and spider web-shaped nuclei. An occasional such cell contained two nuclei. These groups of cells could not definitely be interpreted as Aschoff bodies. Other fields showed a moderate amount of red staining material engulfing cellular elements. The muscle fibers throughout showed marked degenerative changes. The endocardium in many places was markedly thickened and infiltrated with lymphocytes and endothelial cells. The pericardium showed no histopathologic change. The diagnosis was (1) subacute and chronic myocarditis, (2) marked hypertrophy and dilatation of the heart (right and left ventricle), (3) mural thrombi in the right auricle and left ventricle, (4) recent infarct of the left kidney, (5) old infarct of the spleen, (6) multiple emboli in branches of the pulmonary artery, (7) recent infarcts of both lungs, (8) chronic passive hyperemia of the lungs, liver, spleen, and kidneys, and (9) hydrothorax, hydropericardium, ascites, and peripheral edema.

CASE 5.—D. D., an 8.5-year-old boy, entered Sarah Morris Hospital on June 10, 1938. One year before entry he had an attack of rheumatic fever. Although joint phenomena disappeared within a few weeks, he remained in bed for five months because of cardiac findings. He was on graded activity and had no cardiac symptoms until two months before entry, when he had the measles. Subsequent to this he progressively developed dyspnea, orthopnea, cough, and peripheral edema, necessitating his entry into the hospital. Physical examination on admission revealed the heart to be enlarged to the left and right. Systolic and diastolic murmurs were heard at the apex. The liver was palpable 5 fingerbreadths below the costal margin, and there was peripheral edema. The blood pressure was 110/70, and the pulse rate was 100. A diagnosis of old rheumatic endocarditis with mitral insufficiency and stenosis, with an acute exacerbation, was made. During his two-week stay in the hospital the diastolic murmur disappeared. The patient's course was rapidly downhill, and he died in heart failure on June 30, 1938.

Post-Mortem Examination of the Heart.—The heart was distinctly enlarged and weighed 300 Gm. The right and left ventricles were dilated. The left auricle was also thickened. The circumferences of the valvular orifices measured as follows: Tricuspid, 8 cm.; pulmonic, 6 cm.; mitral, 9.9 cm.; and aortic, 5.8 cm. The leaflets of the mitral valve were moderately thickened, with a fine scalloping of the edges. The corresponding chordae tendineae were shortened and in spots fused. A row of minute fibrinous excrescences were present on the line of closure of the inferior leaflet. The aortic cusps were somewhat shortened and thickened. The tricuspid and pulmonic valves showed no gross changes. The epicardium presented a fine granularity over the anterior wall of the right ventricle. The endocardium was normal. Histologic examination of the myocardium revealed a considerable amount of fibrillar connective tissue which in some regions was quite cellular. Clear fat spaces were also noted between the muscle bundles. No Aschoff bodies were in evidence in the specimen examined. The striations of the muscle fibers were indistinct. The diagnosis was (1) acute verrucous endocarditis superimposed on old endocarditis of the mitral valve with insufficiency of the valve, (2) chronic valvulitis of the aortic valve with possible slight insufficiency, (3) fibrosis and cloudy swelling of the myocardium, (4) hypertrophy and dilatation of the right and left ventricles and left auricle, (5) acute fibrinous pericarditis, (6) chronic passive hyperemia of the lungs, liver, spleen, and kidneys, and (7) slight hydrothorax, hydropericardium, and hydroperitoneum.

DISCUSSION

In all of these patients, at one time or another, a diastolic murmur was heard at the apex. In most instances it was rumbling in character. In four cases it was not always present. In one case it was accompanied by an apical thrill. In none of these cases at autopsy was there any evidence of anatomic mitral stenosis. As a matter of fact, in three cases the mitral orifice actually exceeded the tricuspid orifice in circumference or was proportionally enlarged. In two cases there was minimal anatomic evidence of aortic regurgitation. The accompanying blood pressures and anatomic evidence indicated that the insufficiency was too small to produce an Austin Flint murmur. In the case with the isolated myocarditis there was no anatomic lesion at the mitral valve. In the other hearts, there was either acute or subacute verrucous endocarditis or older endocarditis with regurgitation.

As to the etiology of the murmurs, various theories have been suggested. Fisher,[1] Phear,[2] Wood and White[6] and Gunewardene[12] suggested that a relative mitral stenosis was produced by a marked increase in size of the left ventricle due to dilatation. Phear,[2] and Wood and White[6] in addition stressed the necessity of forcible heart action in the production of the murmur. Bland, White, and Jones[13] further suggested that vibrations set up by the diastolic filling of a capacious cavity with relaxed and relatively atonic walls might be responsible for the murmur. Kerr[16] believed that the apical diastolic murmurs heard in the acute stage of rheumatic fever, in severe anemias and leucemias, are due to relative insufficiency of the pulmonary valve. This he[18] explained might result from a mechanical impingement of the dilated pulmonic ring on the mitral ring leading to narrowing of the latter. Sheldon[8] suggested that the murmur was produced when the ventricle sucked blood from the auricle through a thickened or stiffened mitral valve during diastole. Fishberg[17] attributed this murmur to early rheumatic changes in the mitral leaflets which diminish their flexibility so that blood currents set them in audible vibrations.

The common anatomic characteristics in our series are (1) marked dilatation of all the chambers of the heart and (2) myocardial lesions (either an active myocarditis or fibrosis). The absence of any anatomic findings of the mitral valve in one heart definitely refutes Sheldon's theory. Against Kerr's theory is the absence of any marked dilatation of the pulmonic orifice at post-mortem examination. In addition, in the terminal stages, when we should expect the pulmonic insufficiency to be greatest the murmur in several cases disappeared. The anatomic evidence of dilatation of the left auricle and ventricle and the myocardial disease suggest that the most plausible explanation is the production of a relative mitral stenosis by the dilatation of the adjacent chambers. The disappearance of the murmur terminally in two cases suggests that

a certain amount of myocardial power is necessary for the production of the murmur as Phear suggested. The possibility of vibrations of a capacious cavity of course cannot be excluded. We would tend to minimize the possibility of a relative aortic regurgitation producing an Austin Flint murmur, for it is the general consensus of opinion that it requires considerable aortic regurgitation to produce this murmur[15] and in none of our cases were the signs of a marked aortic insufficiency present. The possibility that a previously present mild mitral stenosis was obliterated by the terminal dilatation of the orifice is excluded, for this could not be present in the isolated myocarditis without mitral disease. Fishberg's suggestion certainly could not explain the murmurs arising in our case of isolated myocarditis or in Gunewardene's cases.

Clinically, certain criteria have been accepted as aids in the diagnosis of mitral stenosis. In all the cases reported there was other evidence which supported the presence of stenosis, in addition to the auscultatory findings. A definite diastolic thrill was present in one case. P_2 was accentuated in all cases. Auricular fibrillation was present in two cases. Electrocardiographic changes, such as enlarged P waves, right axis shift or ventricular preponderance, were present in all cases. Fluoroscopic and roentgenologic examination always showed left auricular enlargement. In two of our cases the left auricle formed part of the right heart border, an accepted view of marked left auricular enlargement. In one of our cases hoarseness developed which has been described in rare cases of mitral stenosis.

Certain circumstances will aid in avoiding an incorrect diagnosis of mitral stenosis. In the presence of marked cardiac enlargement, especially if the case has been followed for only a short time, there should be a hesitancy in making a definite diagnosis of mitral stenosis. It cannot be overemphasized that stenosis usually takes several years to develop. Finally, as in Cases 1 and 2, there are patients with rheumatic heart disease who never fully recover from their initial attack or are constantly being reinfected at short intervals. In such patients a diastolic murmur may appear, as it frequently does in acute rheumatic fever, and it may persist for years. In this type of case the probability of the absence of mitral stenosis should be considered.

The occurrence of such cases is probably more frequent than is generally believed. Bland, Jones, and White[14] have reported a series of eighty cases in which diastolic murmurs have been present for years only to disappear and never reappear. In our report five cases are reported in which complete post-mortem examination demonstrated conclusively the absence of mitral stenosis.

CONCLUSION

Five cases of clinically present apical diastolic murmurs unaccompanied by mitral stenosis are reported. These cases again demonstrate

that, in the presence of dilated heart chambers, apical diastolic murmurs may be heard in the absence of mitral stenosis or marked aortic regurgitation. The clinical circumstances of this occurrence are discussed. Anatomic evidence is presented indicating that a relative mitral stenosis produced by dilatation of the left auricle and ventricle is responsible for the murmur.

We are indebted to the several physicians of Michael Reese Hospital in charge of these patients for permission to report the cases, to Dr. O. Saphir for reviewing the anatomic findings, and to Dr. L. N. Katz for suggestions during the study and in the preparation of the report.

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EVALUATION OF THE LOCAL VASODILATOR EFFECT OF ACETYL-BETA-METHYLCHOLINE CHLORIDE (MECHOLYL) BY IONTOPHORESIS

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THE production of local hyperemia using choline derivatives by iontophoresis has received considerable clinical trial in recent years. Of the compounds examined, acetyl-beta-methylcholine chloride (mecholyl) has been found to be the most desirable preparation for this purpose.[1, 2] The basis for the belief that this drug has a local vasodilating effect, however, rests primarily upon such indirect proof as the redness of the part, an elevation of skin temperature[3a] and an observed increase in the rate of capillary flow.[3b] The only direct and quantitative measurements were performed by Montgomery and his associates,[4] who found that a significant increase in the rate of blood flow was elicited in the hand and that this persisted for some time after the termination of the procedure.

Since it has been shown that the response of the blood vessels to various types of stimuli is different in the hand from that in other portions of the extremities,[5] it was considered of interest in the present investigation to obtain a more general evaluation of the peripheral vasodilating effect of mecholyl* iontophoresis by studying the changes produced in the forearm, leg, and foot.

METHOD

The experiments were performed upon nine normal subjects. In view of the constancy of the results, a larger series was not considered necessary. Each person, however, was used repeatedly in an attempt to determine the relative role of the density and duration of the current in the production of the blood flow change. In all, the forearm was studied seventeen times, the leg, eight times, and the foot, five times. Blood flow readings, in cubic centimeters per minute per 100 c.c. of limb volume, were obtained by means of the venous occlusion plethysmographic method, the technique being identical in all respects with that previously reported.[6] The water in the plethysmograph (bath temperature) was either 32° or 45° C. In a number of instances, two portions of different extremities were studied simultaneously.

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As in the study by Montgomery and his associates,[4] the plethysmograph, filled with a 0.2 per cent aqueous solution of mecholyl, was utilized as the positive electrode for iontophoresis, while the negative electrode consisted of an asbestos-covered metal sheet which was thoroughly saturated with warm water and applied to the anterior surface of the abdomen. Special precautions were taken to insulate all metal portions of the plethysmograph which might come in contact with the extremity and thus cause an electrical burn. Current densities of 5 to 15 milliamperes, obtained from a 45-volt "B" battery, were used for periods of ten to twenty minutes. In those instances in which the vasodilating effect of the galvanic current alone was studied, the plethysmograph was filled with physiologic saline instead of a 0.2 per cent solution of mecholyl. In the experiments in which two different extremities were placed in plethysmographs, one machine was filled with water and no current was applied, while the other was utilized in the production of mecholyl iontophoresis in the manner described above.

At least fifteen to twenty blood flow readings were obtained, first in a control period of twenty to thirty minutes, then during the time the current was applied, and finally in the one- to two-hour period following. In those instances in which the effect of varying the intensity or duration of the current was studied, the blood flow readings were utilized in the construction of a graph. By means of a planimeter, the magnitude of the excess blood flow, over and beyond the previously determined basal level, was calculated separately for the period of iontophoresis and for that immediately following. By this means an accurate comparison could be made of the magnitude of the blood flow change elicited by each set of experimental conditions.

Besides blood flow studies, blood pressure and pulse rate readings were obtained repeatedly before, during, and after the period of iontophoresis. All objective and subjective symptoms were likewise recorded.

RESULTS

Forearm.—In every instance, mecholyl iontophoresis produced a significant augmentation in the rate of blood flow through the forearm. This began within two minutes after the onset of the procedure and quickly reached a maximum which was maintained for the remainder of the treatment period. On termination of the current, there was a gradual decrease, and a return to the level of the control blood flow within thirty-five to ninety-five minutes afterward (an average of fifty minutes). The findings in Fig. 1*B* are typical of the response. The average maximal increase in flow was 2.5 times the basal level. The application of the galvanic current alone, in the case of the plethysmograph filled with physiologic saline, produced only a very slight increase in forearm blood flow. In those experiments in which two dif-

ferent extremities were studied simultaneously, with only one being subjected to iontophoresis, the other never demonstrated any increase in blood flow.

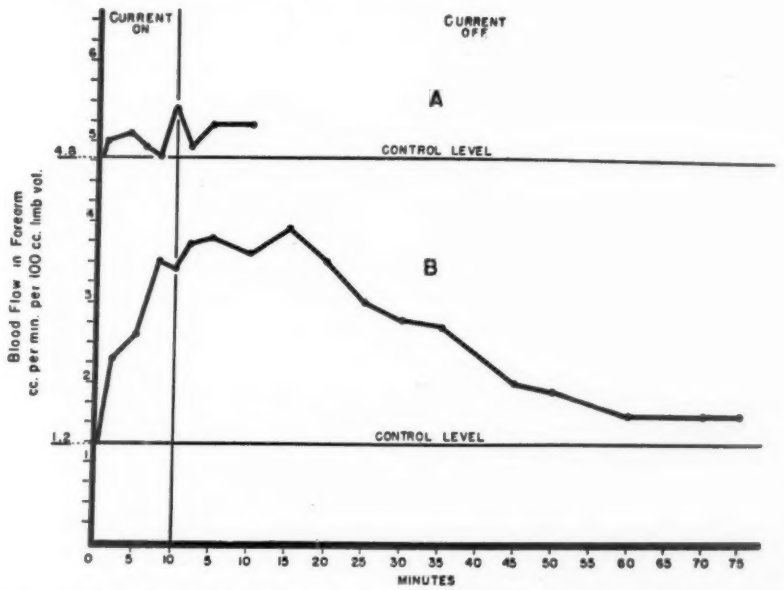

Fig. 1.—Effect of varying the bath temperature upon the blood flow response to a ten-minute period of mecholyl iontophoresis (current density, 15 milliamperes). *A*, Bath temperature, 45° C.; control flow in forearm, 4.8 c.c. per minute per 100 c.c. limb volume. *B*, Bath temperature, 32° C.; control flow in same forearm, 1.2 c.c. Room temperature was 27° C.

Leg.—The vasodilator effect in the leg was less than that in the forearm, the average maximal increase in blood flow being 1.8 times the control flow. The response began within three minutes after the current was turned on, and the increased flow continued for from twenty-one to forty minutes after the treatment was terminated (with an average of thirty-three minutes).

Foot.—The effect upon the foot was comparable to that observed in the forearm. A significant augmentation in the rate of blood flow was uniformly elicited by mecholyl iontophoresis, the average maximal increase being 2.4 times the control level. The augmented blood flow continued for from thirty to ninety minutes after the termination of the iontophoresis (with an average of fifty-eight minutes).

In an attempt to determine the optimal conditions for the blood flow response, the forearm was exposed to a period of ten and then twenty minutes of iontophoresis. Likewise, the effect of a current density of 5 to 7 milliamperes was compared with that observed with one of 12 to 15. No clear-cut evidence was obtained to indicate that the longer period of treatment elicited a greater vasodilator response than the one of shorter duration, and similarly that the higher current density was more efficacious than the lower one. In fact, in the case of each of the two sets of conditions, no significant and consistent difference was noted

either in the highest level of blood flow induced, in the total increase in flow, or in the duration of the augmented circulation in the period following the treatment.

In order to localize the site of action of the drug, the following was performed. The effect of mecholyl iontophoresis was first determined in the forearm at a bath temperature of 32° C., and, after the blood flow had returned to the initial control level, the temperature of the water in the plethysmograph was raised to 45° C. in order to produce maximal vasodilatation of cutaneous blood vessels; the muscle circulation was only slightly affected by such a procedure.[7] When the flow had reached a constant maximal level, mecholyl iontophoresis was again begun. The response in Fig. 1 is typical. It demonstrates that, when the cutaneous vessels are fully dilated by heat, only a small increase in total blood flow is produced by mecholyl iontophoresis.

In order to determine whether or not the vessels in the muscles were capable of being vasodilated under these conditions, the forearm, still exposed to a bath temperature of 45° C., was subjected to a five-minute period of arterial occlusion. Immediately after the release of the pressure, blood flow measurements were obtained during the first minute of reactive hyperemia. In every instance the readings in this period were significantly greater than the previous resting blood flow. Since the skin vessels were already fully dilated by the heat, this increase in total flow during reactive hyperemia was necessarily due to vasodilatation of the blood vessels in the muscle.

In respect to systemic responses, none of any significance was noted in the subjects. At times there was a moderate increase in pulse rate and decrease in blood pressure. At the onset of the iontophoresis, a pins-and-needles feeling was generally experienced locally, but this disappeared within a few minutes. In one subject, 1 c.c. of prostigmin methylsulfate, 1:2,000, was injected subcutaneously about fifteen minutes before iontophoresis was begun, according to the suggestion of Loman and his associates.[8] In this instance, as contrasted with all of the above cases, alarming cardiovascular symptoms appeared. The subject became pale and complained of marked palpitation and a lightheaded feeling; the pulse rate increased very significantly; and the blood pressure decreased.* Although this procedure produced a slightly greater increase in peripheral blood flow as compared with that obtained with mecholyl iontophoresis alone, it was felt that the untoward reactions resulting therefrom mitigated the value of the effect obtained. For this reason, the use of prostigmin in conjunction with mecholyl iontophoresis was considered to have no practical importance, and hence no further studies along this line were attempted.

*The explanation for such results probably rests on the fact that ordinarily with mecholyl iontophoresis a certain quantity of the drug penetrates the skin but is readily destroyed by choline esterase. However, if prostigmin is injected previously so as to inhibit the esterase, then the mecholyl enters the blood stream in sufficient concentration to elicit systemic effects.

DISCUSSION

The use of mecholyl iontophoresis to increase the peripheral circulation appears to be justified by the results obtained in the present investigation on the forearm and foot and by the previous studies of Montgomery and his associates on the hand.[4] However, the findings in the leg would tend to indicate that the procedure does not have as much value if used for the purpose of augmenting blood flow in this region. Of interest in this respect is the observation that nicotinic acid also increases the circulation to the forearm and hand, but has little effect upon the blood vessels in the leg.[9]

The fact that only a slight increase in blood flow was found to occur when the skin vessels were first fully dilated, as by the application of local heat, strongly suggests that under ordinary environmental conditions the effect of mecholyl by iontophoresis is primarily upon cutaneous circulation and that the drug does not penetrate significantly into the muscle layers. The findings that iontophoresis with methylene blue affects only the superficial structures and that the deeper fascia and muscle are unstained even after an application of one hour's duration[10] would be in accord with this view.

On the basis of these observations it is possible to explain, in part at least, the uniformly good results with mecholyl iontophoresis in those states in which the skin circulation is altered, such as Raynaud's syndrome and other vasospastic conditions,[1c, 2] indolent, nonhealing varicose and trophic ulcers,[2, 3a] and scleroderma.[11] Similarly, the reason for the negative, indefinite and equivocal data in the case of diseases of the muscle blood vessels[1c, 2] is also clear, since this procedure does not appear to affect these vessels. Of course, it is possible that this difference may also be related to the occlusive character of the pathologic processes involving the deeper blood vessels.

It is of interest to note that the highest blood flow readings resulting from mecholyl iontophoresis at 32° C. were not as great as those produced merely by raising the temperature of the water in the plethysmograph to 45° C. (Fig. 1). This would imply that mecholyl iontophoresis, in the dosage used, does not produce a maximal vasodilatation of the skin vessels and that it is not as potent an agent in this respect as is heat. It is important to bear in mind, however, that the application of heat to an extremity with diminished blood supply is not without the danger of producing a severe burn. On the other hand, if moderate care is taken in the application of the electrodes, this objection does not hold in the case of mecholyl iontophoresis.

SUMMARY

1. The vasodilating action of mecholyl by iontophoresis was studied in the forearm, leg, and foot of nine normal subjects by means of the venous occlusion plethysmographic method.

2. It was found that this procedure immediately produced a significant increase in the rate of blood flow in the forearm and foot, which continued for some time after the treatment was terminated. The effect upon the leg was less marked.

3. The increase in flow was considered to be primarily the result of vasodilatation of cutaneous blood vessels, those in the muscles probably contributing little if at all to the effect.

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MIXED INFECTIONS IN BACTERIAL ENDOCARDITIS

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THE primary etiologic agent of endocarditis is regarded very generally as a single species of bacteria growing upon the valvular endocardium, and very little emphasis has been laid upon the occurrence of mixed infections with unrelated organisms. Instances of mixed infections in bacterial endocarditis have been reported by Horder,[1] Howell et al.,[2, 3] Blumer,[4] Libman,[5] Thayer,[6] Davis and Weiss,[7] Segal,[8] and Middleton and Burke.[9] Thayer[6] and Davis and Weiss[7] each mentioned one instance in which three distinct organisms were obtained from a single patient. Repeated blood cultures during life positive for two organisms are recorded by Howell et al.,[2, 3] and in another instance[2] a single heart valve vegetation at post-mortem examination yielded two different organisms. Very little comment regarding mixed infections is made, except by Libman[5] and Thayer,[6] who apparently considered such cases as primary bacterial endocarditis of one type with "secondary" or "terminal" infections by other organisms.

Instances of transient "secondary" bacteremias or of "terminal" infections with positive post-mortem cultures of the heart's blood, but not valvular vegetations, have been presented by Wright,[10] DeSanto and White,[11] Martin and Adams,[12] Shiling,[13] Doane,[14] and Khairat,[15] but apparently these authors did not regard such cases as examples of bacterial endocarditis due to several organisms.

It is noteworthy that a review of several series of cases analyzed by Clawson,[16] Kreidler,[17] Horder,[18, 19] Sprague,[20] Fulton and Levine,[21] Musser,[22] Brink and Smith,[23] Capps,[24] Bayles and Lewis,[25] and Christian,[26] in addition to the recent textbooks by White[27] and Levine,[28] failed to disclose any reports of, or comment regarding, mixed infections in bacterial endocarditis.

In view of the fact that we have had the opportunity of observing six patients with bacterial endocarditis, whose blood repeatedly yielded two or more distinct species of bacteria, we feel it sufficiently worthwhile to present brief abstracts of these cases, together with a discussion of the clinical and bacteriologic problems involved.

From July, 1930, to July, 1941, at Duke Hospital, seventy-seven instances of bacterial endocarditis have been observed. In the years 1930

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to 1938, thirty-nine patients with this disease were seen and only one patient (Case 1) had multiple organisms. From 1938 to 1941, in the course of an intensive study of bacterial endocarditis, twenty-eight classical cases were observed clinically and bacteriologically. The blood of five of these patients was repeatedly positive for two or more organisms. In view of the above and the fact that no case diagnosed clinically as bacterial endocarditis has failed to yield positive blood cultures during this period of study, we feel the technique of our method merits a brief review.

In all instances of suspected bacterial endocarditis, blood for culture is taken daily at the height of the fever for four to seven consecutive days. Fifteen to 20 c.c. of blood are obtained by venipuncture from the patient and introduced into a flask containing 4 c.c. of sterile 2.5 per cent sodium citrate solution. The agar in five media tubes (one containing 15 c.c. of 0.1 per cent glucose beef infusion agar, pH 7.4, one containing 15 c.c. of North's gelatine agar, and three tubes containing 15 c.c. of plain beef infusion agar pH 7.4) is melted before the blood is obtained from the patient, and to each of the tubes of molten agar, cooled to 40° C., 2 c.c. of the patient's citrated blood are added, and after being mixed thoroughly, are poured into Petri dishes (one dish for each tube of agar). North's gelatine blood agar (for gonococci) is poured into the top of a Spray dish[29] and incubated in the presence of 10 per cent carbon dioxide. The remaining citrated blood is added to a flask containing 100 c.c. of beef infusion broth, pH 7.4. All of the cultures are incubated at 37° C. The plates are kept for five days, and the flask of broth, for two weeks, before they are reported to be negative. All cultures are examined daily. After the first forty-eight hours' incubation, if no colonies are visible on the plates, 5 c.c. of the supernatant broth are transferred from the flask to a sterile centrifuge tube. After centrifugalization at high speed for fifteen minutes, the supernatant fluid is discarded, a loopful of the sediment is streaked over the surface of each of two blood agar plates and on a slide for a stained smear. One plate is incubated under anaerobic conditions. This procedure is repeated at three-day intervals, until there is sufficient growth for identification. If colonies are present in the poured plates, smears are made of each type of colony (if more than one type is present) and stained by Gram's method. Transplants of the colonies are made to suitable media.

In most instances the organisms, isolated from the present group of patients, grew in the poured plates of the routine cultures of the blood. Because gonococcal endocarditis was suspected in Case 3, three cultures were planted in North's gelatine agar and in ascitic fluid dextrose broth, pH 7.4. A Gram's stain of the broth revealed gram-positive cocci in chains and gram-negative diplococci. Transplants were made to three North's gelatine blood agar plates, one of which was incubated aerobically, and one anaerobically; the third was incubated in the presence

of 10 per cent carbon dioxide. The streptococcus grew only in the anaerobic culture, and the gram-negative diplococcus grew only on the plate incubated in the presence of 10 per cent carbon dioxide. The organism was identified as *Neisseria gonorrhoeae*. Subsequent cultures were incubated both anaerobically and in the presence of 10 per cent carbon dioxide.

A Gram's stain of the hemolytic colonies in the poured plates of the blood of Case 2 revealed pleomorphic gram-negative rods suggestive of the Hemophilus group of organisms. Transplants were made to broth containing the "X" and "V" growth promoting factors. This organism was identified as *Hemophilus para-influenzae*.[30]

The aerobic streptococci were classified according to Brown's[31] and to Sherman's[32] criteria.

REPORT OF CASES

CASE 1. *History.*—P. T., a 52-year-old white business executive and engineer, was admitted to Duke Hospital on Sept. 10, 1932, complaining of fever of one month's duration. His past history revealed typhoid fever and frequent malarial chills as a young man, frequent colds prior to an antrum operation at 37, and mild prostatic symptoms for two years. His present illness began on Aug. 14, 1932, one month before entry, when he developed rather suddenly severe headache, malaise, and fever without chills. His fever continued at a level of 99° F. to 102° F., and pains in his legs and arms appeared. He entered the hospital for diagnosis, because of persistent fever, fatigue, and malaise.

Physical Examination.—The temperature was 38° C.; the pulse rate was 68; and respirations were 20. Examination revealed a well-developed, slightly undernourished white man of 52 in no obvious discomfort. His skin and mucous membranes were clear; no petechiae were observed. The eyes, ears, nose, mouth, and throat showed only enlarged tonsils and a dark left maxillary antrum on transillumination. The neck revealed no abnormalities. The lungs were perfectly clear. The heart was normal in size, shape, and rhythm. No definite murmurs were audible. The peripheral vessels were soft. The abdomen was normal, except for a well-healed appendectomy scar. The spleen was not felt. The genitals were normal. The prostate was diffusely enlarged. The prostatic secretion yielded many white blood cells. The finger tips and toes were very painful to pressure. Neurologic examination was negative.

Laboratory Data.—The hemoglobin was 76 per cent; the red blood cell count, 3,750,000; and the white blood cell count, 9,500, with 79 per cent polymorphonuclear leucocytes. The blood Wassermann reaction was negative. Urinalysis showed only a few white blood cells. Nasal cultures were positive for *Staphylococcus aureus* and prostatic cultures for *Staphylococcus albus*. Roentgenograms of his teeth showed no abscesses. The left antrum and ethmoids were cloudy, interpreted by the roentgenologist as old thickened membrane. Teleroentgenogram revealed normal lungs and heart. Initial cultures of the blood revealed *Streptococcus hemolyticus;* later cultures yielded both *Streptococcus hemolyticus* and *Streptococcus viridans.*

Course in the Hospital.—The patient was placed at bed rest and was given a normal diet and multiple blood transfusions. The first four cultures of the blood, taken between September 13 and 21, yielded only *Streptococcus hemolyticus* (three to ten colonies per cubic centimeter), but on September 22, a blood culture grew out four colonies each of *Streptococcus hemolyticus* and *Streptococcus viridans,* and three subsequent cultures were positive for both organisms (one to ten colonies per cubic centimeter of the former, and four to ten colonies per cubic centimeter of the

latter). The patient stayed in the hospital eighty-eight days, and in spite of blood transfusions, antistreptococcic serum, and sodium cacodylate, his course was steadily and progressively downhill. His fever was persistently elevated, generally between 38° C. to 39° C., rising to 40° C. to 41° C. with chills. Gradually he developed multiple emboli, a palpable spleen, clubbed fingers, systolic and diastolic mitral murmurs, an aortic diastolic murmur, a typical Corrigan pulse, and severe anemia. He was discharged on Dec. 7, 1932, to return home, where his course was rapidly downhill. Death occurred on Jan. 14, 1933, five months after the onset of his disease. No autopsy was obtained.

Final Diagnosis.—Bacterial endocarditis due to *Streptococcus hemolyticus* and *Streptococcus viridans* involving the mitral and aortic valves.

Summary.—This case was very interesting because of the age of the patient, older than average, the fairly sudden onset of his disease, and the absence of a demonstrable heart lesion at entry. The painful fingers and toes, suggesting peripheral emboli, were the outstanding physical findings pointing to endocarditis. The fact that the first four blood cultures taken during the fifth week of his disease were positive for *Streptococcus hemolyticus* might indicate this organism as the "primary" etiologic agent, with "secondary" invasion of the vegetation by *Streptococcus viridans*, which appeared in four subsequent cultures along with the former organisms. No clinical features were present to indicate a mixed infection. *Streptococcus viridans* infection could not be called a "terminal" infection, since it appeared during the seventh week of the disease. The course of the infection was typical of endocarditis, but not specifically of any distinctive type, being longer than acute endocarditis due to a pyogenic organism, and slightly shorter than the usual case of subacute *(Streptococcus viridans)* endocarditis.

CASE 2. *History.*—Miss F. C., a 21-year-old single, unemployed, white woman entered the hospital on June 25, 1938, complaining of weakness of three months' duration. The past history was of interest in that at the age of 12 she had had classical rheumatic fever involving multiple joints for three months. During the intervening nine years she had had little difficulty, save for transient joint pain five years before entry, and slight to moderate diminution in cardiac reserve. Her present illness began in February, 1938, five months before admission, when she developed a febrile illness, with unproductive cough and night sweats. Her convalescence was rapid and uneventful, but in March, 1939, she relapsed, with increasing weakness, general malaise, low-grade fever, and left upper quadrant pain along with tenderness in the finger tips. She was forced to bed three months before entry, because of weakness and weight loss of undetermined amount, and hospitalization was advised because of one blood culture positive for *Streptococcus viridans.*

Physical Examination.—The temperature was 38° C.; the pulse rate was 120; and respirations were 22. Examination revealed a fairly well-developed, but undernourished, chronically ill young white girl, bright and cooperative, in no real distress. Her skin was dry, pale, and delicate. Petechiae were present in the right conjunctiva, the left forearm, and beneath the nail of the left little finger. The eyes, ears, nose, mouth, and throat exhibited a tiny flame-shaped hemorrhage in the left optic fundus and enlarged tonsils. The neck was normal. The lungs were clear. The heart was enlarged to the left; the apex was localized in the fifth intercostal space 10.5 cm. from the midsternal line. By percussion there was prominence of the left upper arc. A marked systolic thrust and a late diastolic thrill were palpable over the precordium. At the apex the first sound was accentuated, and systolic and mid and late diastolic murmurs were audible. Faint systolic and early diastolic murmurs were heard over the aortic area. The rhythm was normal. The blood pressure was 112/54. The pulse was soft and Corrigan in type. The abdomen was relaxed; the right kidney was easily felt, and the spleen was palpated 3 fingerbreadths below the

left costal margin. Pelvic and rectal examinations were not abnormal. The extremities revealed clubbing of the fingers. The reflexes were physiologic.

Laboratory Data.—The hemoglobin was 51.6 per cent; the red blood cell count, 2,940,000; and the white blood cell count, 5,250, with 63 per cent polymorphonuclear leucocytes. The sedimentation rate was 32 mm. per hour, corrected. While the admission urine was entirely negative, later analyses showed a few red blood cells and positive benzidine reactions. Blood nonprotein nitrogen was 25 mg. per cent. Stool examination was essentially negative. Teleroentgenogram showed moderate cardiac enlargement. An electrocardiogram was normal, except for slurring of the QRS complexes in Lead I. Blood cultures were positive for *Streptococcus viridans* and *Hemophilus para-influenzae* (hemolytic). Agglutinins were present initially in the blood serum in dilutions of 1:40 for the former and 1:20 for the latter organism. These titers rose later to 1:80 and 1:160, respectively.

Course in the Hospital.—The patient was placed at bed rest and was given a soft diet with supplementary vitamins, iron, liver, and repeated blood transfusions. During the first two weeks in the hospital her temperature fluctuated daily from 37° C. to 39.8° C. Fresh crops of petechiae developed, and she had one chill, the temperature rising to 40° C. Seven consecutive cultures of the blood were positive for *Streptococcus viridans* (one to eighteen colonies per cubic centimeter) and *Hemophilus para-influenzae* (hemolytic) (one to twenty-six colonies per cubic centimeter). On July 1, she was given 25 c.c. of anti-influenzal serum intravenously, followed by an anaphylactic reaction, which responded satisfactorily to adrenalin, coramine, and oxygen. Five days later she was given 340 c.c. of the same serum intramuscularly without reaction. On July 7, serum sickness developed, and on the same day 88 c.c. of 1 per cent aqueous solution of methylene blue were administered intravenously, followed by a generalized burning sensation, sweating, and blueness of the skin, lasting several days. She was discharged against advice on July 9, twenty-four days after admission, unimproved. Five blood cultures (a total of twelve) meanwhile were consistently positive for *Streptococcus viridans* and *Hemophilus para-influenzae* (hemolytic). A specimen of blood for culture, sent to us after her discharge on July 21, was still positive for both organisms. Death occurred while the patient was at home on Sept. 2, 1938, about seven weeks after discharge. No autopsy was obtained.

Final Diagnosis.—Rheumatic carditis, inactive, with cardiac enlargement, mitral stenosis and insufficiency, and aortic insufficiency. Bacterial endocarditis due to *Streptococcus viridans* and *Hemophilus para-influenzae* (hemolytic) superimposed on aortic and probably mitral valves.

Summary.—Of interest in this case were the presence of pre-existing inactive rheumatic heart disease with mitral and aortic valve lesions, the onset of her disease with fever and symptoms from the respiratory tract, indicating the probable portal of entry of the organisms, and the blood cultures (a total of 13), repeatedly positive for both *Streptococcus viridans* and *Hemophilus para-influenzae* (hemolytic). There were no features by history, physical examination, or clinical course to suggest a "primary" organism, or even to suggest the presence of a mixed infection, yet the repeatedly positive blood cultures, uninfluenced by therapy leave little doubt that both organisms were present in the heart valve vegetations and were etiologically important.

CASE 3.* *History.*—Mrs. S. C., a 24-year-old white housewife, was admitted to Duke Hospital on Sept. 25, 1938, complaining of fever with chills for about three months. Three months before entry during a normal pregnancy, she developed very suddenly chills, high fever, and multiple painful swollen joints, which later subsided, except for continued swelling of the left knee. Paracentesis of the joint yielded

*This case was reported in detail previously by the authors, New England J. Med. 221: 167, 1939.

purulent fluid but no organisms. A blood culture was negative at this period, but a gonococcal complement fixation test was 4+. Spontaneous delivery of a normal child was followed by a brief remission of her symptoms. However, she soon relapsed with irregular recurring chills, high fever, marked sweating, gradual weight loss, and partial ankylosis of the knee. An adequate course of sulfanilamide and three blood transfusions were administered without therapeutic effect, prior to hospitalization here.

Physical Examination.—The temperature was 39.8° C.; the pulse rate was 116; and the respirations were 24. Examination revealed a pallid, slender, poorly developed, undernourished white woman of 24, who appeared acutely ill. The skin was pale, but warm and there were no petechiae nor emboli. The spine and lymphatic systems were not remarkable. The eyes, ears, nose, mouth, and throat were normal, except for hypertrophied, infected tonsils. The cervical veins were not distended. The lungs presented a few fine crepitant râles after cough at the angle of the right scapula. The heart's apex was in the fifth intercostal space 9 cm. from the midsternal line, indicating slight but definite cardiac enlargement. At the apex a faint protodiastolic gallop rhythm was present. Over the pulmonary area, a soft systolic murmur and a high-pitched, early, pulmonary diastolic murmur, transmitted to the third interspace, were heard, and P_2 was accentuated. The rhythm was regular. The peripheral arterial walls were soft. The blood pressure was 100/70. The abdomen was normal; the spleen was not felt. Pelvic examination revealed erosive cervicitis. The left knee showed partial ankylosis. No clubbing of the fingers or of the toes was evident.

Laboratory Data.—The hemoglobin was 60 per cent; the red blood cell count, 3,050,000; and the white blood cell count, 10,500, with 78 per cent polymorphonuclear neutrophiles. Repeated urinalyses revealed a few white blood cells. Sedimentation rate was 37 mm. per hour, corrected. Blood Wassermann test was negative. Gonococcal complement fixation test was 4+ on two occasions. An electrocardiogram was normal. Teleroentgenogram revealed an infarct in the right lung, and a globular heart with slight enlargement. Cervical smears and cultures were negative for *Neisseria gonorrhoeae*. Repeated blood cultures were positive for *Neisseria gonorrhoeae* and a non-hemolytic anaerobic streptococcus.

Course in the Hospital.—The patient was placed at strict bed rest and given a high-vitamin diet, iron, liver, and repeated blood transfusions. During the first five hospital days, daily chills with fever rising to 38.7° C. to 40.4° C. were evident, and five consecutive blood cultures, taken daily at the height of fever, were positive for *Neisseria gonorrhoeae* and a nonhemolytic anaerobic streptococcus, the colony counts being less than one colony per cubic centimeter of blood in each instance. Sulfapyridine was administered orally in gradually increasing doses from 1.2 to 5 Gm. per day for fifty-two days. The temperature fell abruptly to normal and rose to 39.5° C. on the twelfth day of therapy. A blood culture yielded the anaerobic streptococcus, but was negative for *Neisseria gonorrhoeae*. Eight days later, the temperature rose again to 38° C., but the blood culture was negative and three subsequent cultures, taken at weekly intervals thereafter, were all negative. She remained afebrile and asymptomatic throughout the remainder of her hospital stay, felt well, and gained in weight and strength. She was discharged well, on Nov. 27, 1938, sixty-three days after entry. Opsonins, agglutinins, and bactericidins, initially absent or in low titer, appeared and increased to high titer for both organisms at the time of discharge. The gonococcal complement fixation test, initially 4+, became negative. Re-examinations at intervals of approximately one and four months after discharge revealed the patient well, the pulmonary murmur persisting, and blood cultures entirely negative. The patient was last heard from by letter in January, 1940, and reported her health as excellent.

Final Diagnosis.—Bacterial endocarditis due to *Neisseria gonorrhoeae* and a nonhemolytic anaerobic streptococcus involving the pulmonary valve.

Summary.—A classical example of bacterial endocarditis involving the pulmonary valve is presented. The fact that five consecutive cultures of the blood were positive for two organisms, *Neisseria gonorrhoeae* and a nonhemolytic anaerobic streptococcus, suggests that both organisms were probably present in the bacterial vegetations on the pulmonary valve. The clinical history was quite typical of gonococcal endocarditis, and there were no features, except for the positive blood cultures to suggest the presence of a mixed infection. It should be noted that under sulfapyridine therapy the gonococcus disappeared from the blood stream prior to the anaerobic streptococcus. While this indicates greater sensitivity of the gonococcus to the drug, it may indicate also that the streptococcus organisms were deep in the vegetations rather than superficially located, and certainly demonstrates the necessity of drug therapy, adequate to eradicate both organisms, before cure of the patient can be effected.

CASE 4. *History.*—H. E., a 21-year-old, unoccupied, white woman was admitted to Duke Hospital on Jan. 5, 1939, complaining of pain in the left upper quadrant of her abdomen for three days. Her past history revealed that she had had a "leaking heart" since early childhood, but there was no history of rheumatic fever, chorea, scarlet fever, or tonsillitis. Her present illness began one month before admission, when she developed malaise, weakness, and fever without chills. She was hospitalized elsewhere for two weeks, and a diagnosis of rheumatic fever was made. Three days prior to admission here she developed sudden severe sharp pain beneath the left costal margin aggravated by inspiration and cough. Her fever had been relatively constant, and weight loss of indeterminate amount had been noted.

Physical Examination.—The temperature was 39° C.; the pulse rate was 90; and respirations were 20. Examination revealed a well-developed but slender, swarthy, attractive girl of 21, complaining of pain in the left flank. The skin was hot and dry. No petechiae were noted. The mucous membranes were pale. The eyes, ears, nose, mouth, and throat were not remarkable, except for enlarged tonsils, and a reddened pharynx. The neck veins were prominent, and the thyroid was symmetrically enlarged. The lungs were clear. The heart was enlarged slightly to the left, the apex being in the fifth intercostal space 8.5 cm. from the midsternal line. At the apex there was a systolic thrill, a harsh blowing systolic murmur and a late diastolic murmur. The rhythm was normal. The pulse was soft. The blood pressure was 110/70. The abdomen showed exquisite tenderness in the left upper quadrant where the spleen was just palpable and tender. A friction rub was heard over the splenic area. Pelvic and rectal examinations were normal. The extremities were not remarkable. The reflexes were normal.

Laboratory Data.—The hemoglobin was 60 per cent; the red blood cell count, 2,900,000; and the white blood cell count, 9,520, with 86 per cent polymorphonuclear leucocytes. The sedimentation rate was 36 mm. per hour, corrected. Repeated urinalyses showed only one to three white blood cells per high-power field in uncatheterized specimens. The blood Wassermann and Kahn reactions were negative. Stool examination was negative. Fluoroscopy of the chest and teleroentgenogram showed obliteration of the left costophrenic angle by a small amount of fluid, and generalized cardiac enlargement, with rapid weak pulsations. A flat plate of the abdomen was negative. Two electrocardiograms were abnormal due to slurred QRS complexes in Lead I, and inversion of T_1 and T_2, and diphasic T_4. Blood cultures were positive for *Streptococcus fecalis* and *Streptococcus hemolyticus.* Initial studies of immune antibodies revealed negligible phagocytosis and negative agglutinations. Subsequent studies showed slight phagocytosis, and agglutination titers to both organisms in serum dilutions of 1:1280.

Course in the Hospital.—She was placed at bed rest and given a high-caloric, high-vitamin diet, supplemented with liver and iron. A total of eleven blood transfusions was given during her hospital stay. During the first week in the hospital her temperature was persistently elevated with swings from 37.4° C. to 39.8° C., and five consecutive blood cultures were positive for *Streptococcus fecalis* (four to thirteen colonies per cubic centimeter) and *Streptococcus hemolyticus* (seven to twenty-six colonies per cubic centimeter). On January 9, she was started on sulfapyridine, 4 to 5 Gm. daily for a period of twenty-three days, during which time her temperature dropped very slightly. Six of seven cultures of the blood taken during this interval were negative for *Streptococcus hemolyticus*, but all were positive for *Streptococcus fecalis*. Therapy was then shifted to neoprontosil intramuscularly and orally for a period of ten days. A high fever returned, and three cultures were positive for both organisms during prontosil therapy. On February 12 (thirty-eighth hospital day), the patient was given sodium sulfanilyl sulfanilamide in doses of 3 Gm. daily for one week without effect. On February 15, for a period of four days the patient was given 200 c.c. of polyvalent antistreptococcic serum, without benefit, and on February 26, 200 c.c. of anti-enterococcic serum were given, without reaction. Subsequently sulfapyridine and sodium sulfapyridine were given orally in large doses (9 Gm. per day) without benefit. She continued febrile, with repeated emboli, and sixteen blood cultures (a total of thirty-one) were positive for *Streptococcus fecalis* and *Streptococcus hemolyticus*. On March 5, because of severe right lower quadrant pain, an appendectomy was performed, and a normal appendix was removed, and only numerous petechiae were found in the intestinal wall. Her white blood cell count and sedimentation rate remained elevated during her entire period of hospitalization. In view of failure of improvement, the patient was discharged on April 4, 1939. No follow-up notes are available, with regard to her further course.

Final Diagnosis.—Rheumatic carditis, inactive, with slight cardiac enlargement, mitral stenosis and insufficiency. Bacterial endocarditis due to *Streptococcus fecalis* and *Streptococcus hemolyticus* superimposed on the mitral valve.

Summary.—The patient presented rheumatic heart disease with mitral stenosis and insufficiency with the onset of bacterial endocarditis, one month prior to entry. There was no indication by history of the portal of entry, nor of the specific organism responsible for the disease. The disclosure of five consecutive blood cultures, positive for *Streptococcus fecalis* and *Streptococcus hemolyticus* in significant numbers, early in the disease one month after onset, in the absence of any other focus of infection suggests that both organisms were etiologically responsible for the bacterial endocarditis. The therapeutic import of this fact is revealed by the disappearance of the *Streptococcus hemolyticus*, but not the *Streptococcus fecalis* under sulfapyridine therapy, and the later blood cultures positive for both organisms. It is to be noted that the re-exhibition of sulfapyridine did not affect the *Streptococcus hemolyticus*, which meanwhile had become "sulfapyridine fast." It would seem that both organisms must be removed if endocarditis is to be cured, since temporary sterilization of but one organism is generally followed by the reappearance of that organism at a later date when therapy is discontinued.

CASE 5. *History.*—Mrs. O. C., a 45-year-old white housewife, was admitted to Duke Hospital on Dec. 31, 1939, complaining of fever of eight months' duration. Her past history revealed the presence of a "heart murmur" with mild dyspnea on exertion for twenty-seven years and scattered, poorly localized, transient muscle and joint pains, for four years. Her present illness began insidiously eight months before admission with the gradual onset of malaise, weakness, anorexia, intermittent fever without chills, and generalized muscle pains, most marked in the cervical region. Progressive weight loss and general decline in health followed. Several abscessed teeth were removed three months before entry with striking exacerbation of her

symptoms, and emboli were noted to fingers, toes, and spleen. A course of sulfanilamide was given without benefit. By the time of admission to the hospital she had lost 25 pounds in weight.

Physical Examination.—The temperature was 39.5° C.; the pulse rate was 100; and the respirations were 22. Examination revealed a well-developed, poorly nourished, almost emaciated white woman of 45, who appeared chronically ill, complaining of pain in the left lower chest. The skin, spine, and lymphatics showed nothing remarkable, except for a fatty tumor of the left thigh, and several small, bruised areas on both legs. Petechiae were evident in the right conjunctiva. The eyes, ears, nose, mouth, and throat revealed only dental repair and extractions, and pallor of the mucous membranes. The neck exhibited muscle stiffness and pain on motion. The cervical veins were not distended. The lungs contained transient râles at the left base where a faint friction rub was audible. The heart was enlarged to the left, the apex being in the fifth intercostal space 10.5 cm. from the midsternal line; prominence of the left upper arc by percussion was noted. A loud harsh systolic murmur and a late rumbling diastolic murmur were audible over the apex. P_2 was accentuated and greater than A_2. No basal murmurs were heard. The rhythm was regular. The blood pressure was 140/90. The peripheral vessels were normal. Abdominal examination revealed the liver and spleen to be palpable just below the costal margins. There was a well-healed midline scar, and tenderness in both upper quadrants. The pelvic and rectal examinations were normal. The fingers and toes were quite tender, with early clubbing. The reflexes were physiologic.

Laboratory Data.—The hemoglobin was 85 per cent; the red blood cell count, 4,370,000; the white blood cell count, 12,750, with 87 per cent polymorphonuclear neutrophiles. The sedimentation rate was 36 mm. per hour, corrected. Urinalysis showed a trace of albumin, one or two white blood cells, one or two red blood cells, and an occasional hyaline cast per high-power field. Stool examination was negative. Blood Wassermann and Kahn reactions were negative. Teleroentgenogram revealed the lungs to be clear. The heart was greatly enlarged to the left, and the left auricle was dilated. The electrocardiogram was abnormal, due to slurred QRS complexes, ventricular premature beats, and inverted T_3. Repeated blood cultures were positive for *Streptococcus viridans* and *Streptococcus hemolyticus.*

Course in the Hospital.—The patient was placed at bed rest and was given a high-vitamin diet, with supplementary vitamins, iron, liver, and repeated blood transfusions. During the first week in the hospital, her temperature was persistently elevated with peaks from 38° C. to 39° C., and six consecutive cultures of the blood were positive for *Streptococcus viridans* (two to thirty-eight colonies per cubic centimeter), and *Streptococcus hemolyticus* (one to thirty-four colonies per cubic centimeter). On the eighth and ninth hospital days, single test doses of 4 Gm. of sodium sulfapyridine were administered intravenously. A blood culture was still positive for *Streptococcus viridans* (four colonies per cubic centimeter) and *Streptococcus hemolyticus* (less than one colony per cubic centimeter). On the tenth and eleventh days, 6 and 12 Gm. of sodium sulfapyridine were given intravenously, the blood concentrations rising to 19.8 mg. per cent and 24 mg. per cent, respectively. A blood culture taken twelve hours later was sterile, and eighteen subsequent cultures taken biweekly until the patient's discharges were all negative, except for one obviously contaminated blood culture. The temperature dropped to normal after the fourth intravenous drug injection and except for occasional rises to 37.9° C. remained normal during the patient's entire hospital stay. Oral administration of the drug in doses of 10 Gm. per day at four-hour intervals was then substituted, the blood concentrations averaging 9.9 mg. per cent. She tolerated the drug poorly and gradual fall in weight of 6 kg. was noted. Under continued drug therapy, progressive anemia, in spite of repeated transfusions, was manifested. The white blood cell count fell to normal by the twenty-fifth day, but the sedimentation rate remained

very active. With the disappearance of the bacteremia, immune antibodies for both organisms appeared in the patient's blood in moderately high titer by the time of discharge. The patient left the hospital against advice on Feb. 24, 1940, the fifty-fifth hospital day, after forty-eight days of continuous therapy. She was discharged on sulfapyridine, 5 Gm. daily. Her physician reported gradual decline in health, with fever, toxemia, cardiac dilatation, cardiac failure, and death in May, 1940, three months after discharge. No autopsy was obtained. A specimen of blood for culture sent to us on April 23, 1940, was positive for *Streptococcus viridans* (six colonies per cubic centimeter) and *Streptococcus hemolyticus* (less than one colony per cubic centimeter). Tests for immune bodies in the blood serum revealed a marked reduction in titers of agglutinins and bactericidins.

Final Diagnosis.—Rheumatic carditis, inactive, with cardiac enlargement, mitral stenosis, and insufficiency. Bacterial endocarditis due to *Streptococcus viridans* and *Streptococcus hemolyticus* superimposed upon the mitral valve.

Summary.—This patient exhibited the common clinical background of bacterial endocarditis (i.e., rheumatic heart disease with mitral stenosis and insufficiency) and her history and subsequent course were quite typical of *Streptococcus viridans* endocarditis. There were no features to suggest a *Streptococcus hemolyticus* infection, nor a mixed infection, but the presence of six consecutive cultures of the blood, prior to therapy, positive for both *Streptococcus viridans* and *Streptococcus hemolyticus* in significant numbers, very definitely suggests that both organisms were present in the heart valve vegetations. The disappearance of both organisms simultaneously under therapy and their reappearance after the discontinuance of therapy, in the absence of any other demonstrable focus, is evidence of the etiologic importance of both organisms.

CASE 6. *History.*—Mrs. A. S., a 51-year-old housewife, was admitted to Duke Hospital on Jan. 14, 1941, complaining of weakness of three months' duration. Her present illness began in October, 1940, three months prior to admission, when she developed fever and chills, and shortly thereafter, cough productive of small amounts of blood, dyspnea, and increasing weakness. Anorexia, nausea, vomiting and hematuria followed. One month after onset she was hospitalized by her own physician, because of weakness, high fever, and recurrent chills. A brief remission in chills followed two blood transfusions. She was referred to this hospital because of persistent fever, chills, weakness, and weight loss of 40 pounds within three months.

Physical Examination.—The temperature was 36.8° C.; the pulse rate was 100; and respirations were 18. Examination revealed a pallid, emaciated white woman of 51, who was acutely ill. The skin and mucous membranes were pale, and petechiae were scattered over the trunk and limbs and in the right conjunctiva. Examination of the eyes, ears, nose, mouth, and throat revealed pyorrhea of the gums and marginal atrophy of the tongue. The neck veins were engorged. The lungs showed numerous moist râles bilaterally, which were greater on the right, with dullness and diminished breath sounds at the right base. The heart was moderately enlarged with the apex in the fifth intercostal space at the anterior axillary line. A soft, blowing systolic murmur was audible at the apex, but no diastolic murmur was heard. The rhythm was regular. The blood pressure was 120/68. The liver was enlarged to the umbilicus, firm, but tender, and the spleen was felt 3 fingerbreadths below the left costal margin. The pelvic examination was normal, except for relaxation of the pelvic floor and retroversion of the uterus. There was no clubbing of the fingers or of the toes. Neurologic examination was negative.

Laboratory Data.—The hemoglobin was 49 per cent; the red blood cell count, 2,670,000; and the white blood cell count, 7,200, with 86 per cent polymorphonuclear leucocytes. A sedimentation rate, corrected was 14 mm. per hour. Blood Wassermann and Kahn reactions were negative. Repeated urinalyses showed albumin, vary-

ing numbers of red blood cells, a few white blood cells, and granular casts per high-power field. Stool examination was negative. Electrocardiogram showed sino-auricular tachycardia, low voltage, and slurred QRS complexes and flat T waves in all leads. Teleroentgenogram revealed cardiac enlargement and a triangular area of density at the right base obscuring the right costophrenic angle. Stool and urine cultures grew only *Escherichia coli*. Blood cultures yielded *Streptococcus viridans* and *Streptococcus hemolyticus* growing in symbiosis with an unidentified gram-negative rod.

Course in the Hospital.—The patient remained in the hospital twenty-eight days, during which time her temperature was persistently elevated with daily peaks in temperature from 37.8° C. to 39.8° C. She was given a high-vitamin diet, supplemented with iron, liver, and blood transfusions, and was completely digitalized. During the first five hospital days, four consecutive cultures of the blood were positive for *Streptococcus viridans* (three to ten colonies per cubic centimeter of blood) and *Streptococcus hemolyticus* growing in symbiosis with an unidentified gram-negative rod (100 to 228 colonies per cubic centimeter of blood). Sulfadiazine was given orally about 4 Gm. per day for six days, beginning January 21, and 1 to 2 Gm. daily for four days thereafter. On January 22 the sulfadiazine concentration in the blood was 8.8 mg. per cent, and the blood nonprotein nitrogen was 66 mg. per cent. Three consecutive blood cultures taken during sulfadiazine concentrations of 9.2 to 14.2 mg. per cent were positive only for *Streptococcus viridans* (four to ten colonies per cubic centimeter). Sulfadiazine was discontinued on January 30, because the blood nonprotein nitrogen rose to 108 mg. per cent. Meanwhile the patient became weaker, the heart murmur louder, and congestive failure deeper in spite of therapy. Two subsequent blood cultures (on January 27 and on February 10) showed *Streptococcus viridans* (thirty-eight to forty colonies per cubic centimeter) and the mixed organisms noted above (two to 148 colonies per cubic centimeter). On February 7 she developed agranulocytosis, with a white blood cell count of 700; three days later all polymorphonuclear leucocytes had disappeared from the peripheral blood, and the bone marrow was almost entirely devoid of myeloid cells. She went downhill rapidly; coma ensued, with a blood nonprotein nitrogen of 135 mg. per cent; edema progressed. The patient died quietly on Feb. 12, 1941.

Autopsy revealed a typical vegetative endocarditis, with huge greenish vegetations involving the tricuspid valve, and smaller vegetations on the aortic valve, and old rheumatic scarring of the mitral valve and chordae tendinae. Multiple infarcts were present in both lungs, and a large pulmonary embolus involved the superior branch of the right pulmonary artery. Emboli were present in an acute splenic tumor and in both kidneys. Microscopic sections of the vegetations of the heart valves showed the classical findings of bacterial endocarditis with cocci deep in the base of the valvular vegetations. Cultures of the heart's blood and the vegetations from the tricuspid and aortic valves revealed *Streptococcus viridans, Streptococcus hemolyticus,* and the unidentified gram-negative rod.

Final Diagnosis.—Bacterial endocarditis due to *Streptococcus viridans, Streptococcus hemolyticus,* and an unidentified gram-negative rod, involving the tricuspid and aortic valves. Rheumatic carditis, inactive, with old mitral valvulitis.

Summary.—This patient provided data of exceptional interest from the clinical, bacteriologic, and pathologic standpoints. Her history and subsequent course were typical of bacterial endocarditis, complicated by cardiac failure and renal insufficiency. The development of agranulocytosis following sulfadiazine therapy undoubtedly precipitated premature death, although the pathologists felt that pulmonary emoblism from the tricuspid valve vegetations was the actual cause of exodus. The finding of three organisms (*Streptococcus viridans, Streptococcus hemolyticus,* and an unidentified gram-negative rod) in the first 4 consecutive blood cultures was very unusual, although here again there was nothing to suggest the presence of a

mixed infection. The persistence of *Streptococcus viridans* in the blood cultures during therapy suggested only the relative resistance of this species of bacteria to chemotherapy. Of paramount importance in the problem of etiology was the postmortem bacteriologic demonstration of all three organisms in the heart's blood culture and in cultures taken from both aortic and tricuspid valves.

DISCUSSION

The clinical features of six cases of classical bacterial endocarditis, in which blood cultures were repeatedly positive for two or more organisms, have been presented. In five instances two organisms were consistently present, while in the sixth, three organisms were isolated. In two instances (Cases 1 and 5) the organisms were *Streptococcus viridans* and *Streptococcus hemolyticus*, while in the others the organisms were *Streptococcus viridans* and *Streptococcus hemolyticus* growing in symbiosis with an unidentified gram-negative rod (Case 6), *Streptococcus viridans* and *Hemophilus para-influenzae* (hemolytic) (Case 2), *Streptococcus fecalis* and *Streptococcus hemolyticus* (Case 4), and *Neisseria gonorrhoeae* and a nonhemolytic anaerobic streptococcus (Case 3). In the first five instances noted above, the organisms were grown on routine laboratory media, while in the sixth the possibility of *Neisseria gonorrhoeae* was suspected, and appropriate media were employed.

A careful analysis of the history, physical findings, routine laboratory data, and clinical course of these patients reveals little that may be considered distinctive of mixed infections. The necessity for careful bacteriologic studies as the only means of identifying the presence of mixed infections is thus emphasized.

The recognition of such mixed infections in bacterial endocarditis is of fundamental importance in the therapy of the disease, since all organisms must be eradicated from the blood and the heart valve vegetations if cure of the patient is to be accomplished. This is clearly illustrated by Case 3, where both organisms (*Neisseria gonorrhoeae* and anaerobic streptococcus) proved sensitive to a single drug, resulting in recovery, and in Cases 4 and 6, where the *Streptococcus fecalis* and the *Streptococcus viridans* proved resistant to sulfonamide therapy, while the hemolytic streptococci, sensitive in both patients, disappeared from the blood stream temporarily, and later returned after the discontinuance of therapy. Indeed, from the brief experiences reported here, a single organism could not alone be eradicated permanently, for, in each instance after the discontinuance of therapy, the organism, thus temporarily eliminated, returned in cultures before death.

In instances of mixed infections, it seems very certain that both organisms are present not only in the blood but in the vegetations as well. The finding of consecutive blood cultures repeatedly positive for several organisms strongly favors this view, when there is no obvious focus present, other than the heart valve vegetation, to shed organisms into

the blood stream. The demonstration of mixed organisms in the valvular vegetations at autopsy (Case 6) is proof of this assumption. Blood cultures repeatedly positive for the same organisms eliminate the possibility of simple contamination.

When the blood of patients suffering from bacterial endocarditis yields two or more organisms, the question of the specific etiologic relationship of each organism to the disease is an interesting and important one. In the pathogenesis of such cases undoubtedly the valve is first invaded by one organism, and later the vegetations of the first are invaded by the second organism. The determination of which organisms are "primary" and which are "secondary" is extremely difficult in the majority of instances, and in but two of our cases (Case 1 and Case 3) were we reasonably certain that the hemolytic streptococcus and the gonococcus were the "primary" organisms. We do not feel that additional or "secondary" organisms are "terminal" infections, since they have appeared too early in the course of the disease process and particularly since opsonins, agglutinins, and bactericidins, when present, were in about equal titer for both organisms. Regardless of the terminology used in mixed infections, when two or more organisms are present in the vegetations on the heart valves, each must be considered of etiologic significance, because all must be eradicated before cure of the patient can be effected.

CONCLUSIONS

1. Six cases of classical bacterial endocarditis have been presented, in which two or more organisms were cultured repeatedly from the patients' blood.

2. The clinical, bacteriologic, and pathologic aspects of the problem have been discussed.

3. The importance of the bacteriologic demonstration of the presence of mixed infections in bacterial endocarditis is emphasized, because of the etiologic relationship of such organisms to the disease and the therapeutic problem involved.

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A COMPARISON OF ELECTROCARDIOGRAPHIC CHANGES OBSERVED DURING THE "ANOXEMIA TEST" ON NORMAL PERSONS AND ON PATIENTS WITH CORONARY SCLEROSIS

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ALTERATIONS in the form of the electrocardiogram caused by induced anoxemia have been used to estimate the functional efficiency of the coronary circulation. Evidence has been presented indicating that the "anoxemia test" affords an index of the coronary reserve. An apparatus and a technique for performing the test have been described, and criteria for an abnormal response have been proposed.[1-3] If properly done, the procedure is simple and safe. Various unpleasant reactions which may be encountered have been reported.[3] Gilbert and his associates have employed the method in a study of the effects of various drugs upon patients with "angina of effort,"[4, 5] and they have expressed the opinion that "the experiment is perfectly humane and without danger."[4]

In the light of further experience, it seemed desirable to analyze critically the results of tests on normal persons and on patients with coronary sclerosis, with particular reference to differences in the electrocardiographic changes observed in the two groups.

MATERIAL AND METHOD

The analysis is based upon the results of 293 tests, of which 136 were done on persons who were regarded as normal, in the sense that they were free of cardiac disease, and 157, on patients with coronary sclerosis. The criteria for the diagnosis of coronary sclerosis were a history of anginal pain, cardiac enlargement, as shown in the teleroentgenogram, and an abnormal electrocardiogram. The presence of any two of these was considered sufficient. Cases in which there were other possible etiologic factors were not included. The normal group comprised twenty women and 116 men, ranging in age from 21 to 73 years. Of the normal subjects, twenty-eight were over 50 years old, and, of these, four were over 70. The group with coronary sclerosis included 136 patients with a history of anginal pain and forty-three who were known to have healed cardiac infarcts; their ages ranged from 35 to 77 years.

In a number of these cases only one test was performed. When more than one was done, the first was selected whenever possible. No test was included during which there occurred any unusual or unpleasant reaction, such as one of those noted in an earlier paper.[3]

The procedure previously described was employed.[2, 3] The subjects breathed a mixture of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes unless

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cardiac pain was experienced before the end of that time. Four-lead electrocardiograms were taken routinely just before the test was started and at intervals of five minutes thereafter. If the patient complained of discomfort, a record was quickly taken, the low-oxygen mixture was shut off, and 100 per cent oxygen was administered for one minute. The precordial lead used was the one commonly designated as IVF. All electrocardiograms were measured by at least two observers. When the RS-T deviation was measured, the level of the P-R interval was taken as the isoelectric line, and readings were made to the nearest half millimeter. In each test the result was based on the difference between the control and the record showing the maximal changes during induced anoxemia. As will be pointed out, it was not invariably the last electrocardiogram in which the greatest alterations were found.

RESULTS

Occurrence of Pain.—Since none of the normal persons experienced pain, the test lasted the full twenty-minute period in every case. Of the 157 patients with coronary sclerosis, seventy-four (47 per cent) complained of pain, and, in fifty-four (63 per cent) of those who had pain, the discomfort appeared during the first ten minutes (Fig. 1). A positive test was observed in seventy-seven (49 per cent); pain occurred in 27 per cent and was absent in 22 per cent. The test was negative in eighty (51 per cent); pain occurred in 20 per cent and was absent in 31 per cent (Table I). It has previously been pointed out that the occurrence of pain, even in the absence of significant electrocardiographic changes, affords *presumptive* evidence of a diminished coronary reserve. Its appearance during the first ten minutes of a negative test is of particular importance. In a follow-up study of fourteen such cases, four patients later showed a positive test, one had an attack of coronary occlusion, and two died of their cardiac disease.[3] If, then, in this series of 157 cases of coronary sclerosis the positive reactions are added to negatives during which pain occurred, the test furnished evidence of coronary insufficiency, actual or presumed, in 109, or 69 per cent.

TABLE I

INCIDENCE OF PAIN IN 157 PATIENTS WITH CORONARY SCLEROSIS IN RELATION TO THE RESULT OF THE ANOXEMIA TEST

	POSITIVE		NEGATIVE	
	NO.	%	NO.	%
With pain	42	27	32	20
No pain	35	22	48	31
Total	77	49	80	51

Deviation of the RS-T Segments.—No normal person showed a total RS-T deviation greater than 2.5 mm., and in only seven was this figure reached (Fig. 2*A*). In the individual leads, a deviation of 1.5 mm. was observed in one case; a deviation of 1 mm. occurred in twenty-five leads in twenty-one cases. In contrast to the normal group, sixty-two patients with coronary sclerosis developed a total RS-T deviation of

3 mm. or more; in nine of these the change measured more than 5 mm. (Fig. 2*B*). In the individual leads, deviations varied from zero to 5 mm., and a change of 1 mm. or more occurred in 185 leads in ninety-two cases. The average RS-T deviation for each lead in patients with coronary sclerosis was greater than that for the corresponding lead in the normal subjects. The difference was most marked in Leads I and IVF (Fig. 3).

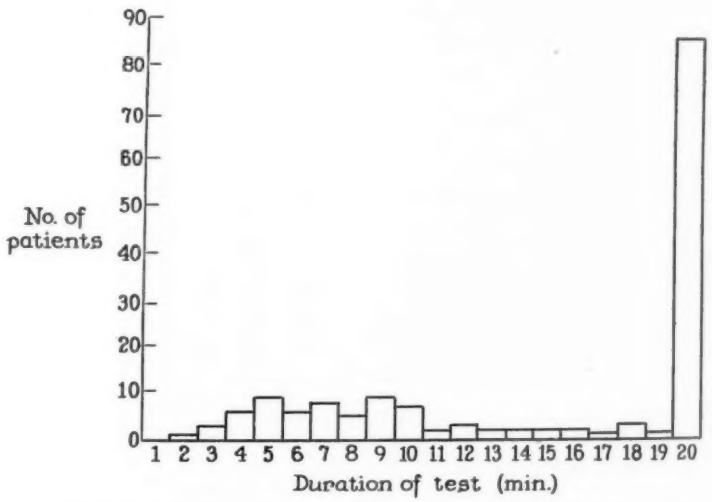

Fig. 1.—Duration of the anoxemia test in 157 cases of coronary sclerosis. Tests shorter than twenty minutes were terminated at the onset of pain.

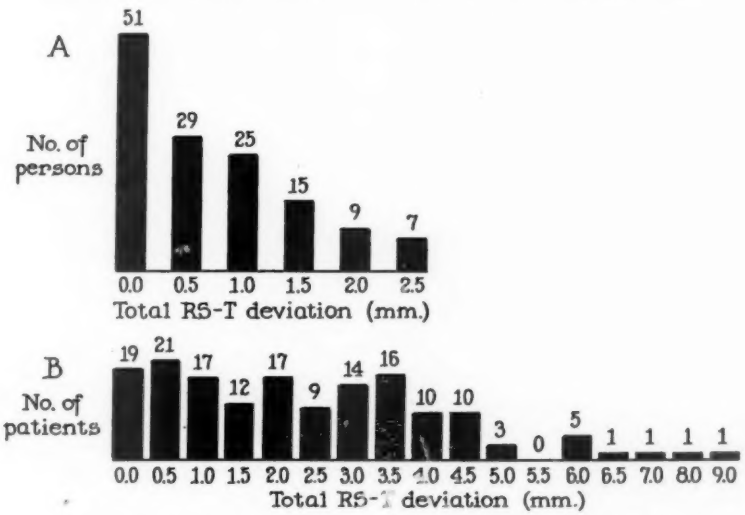

Fig. 2.—Total RS-T deviation which occurred during the anoxemia test. *A*, in 136 normal persons; *B*, in 157 patients with coronary sclerosis.

In many of the cases of coronary sclerosis the total deviation increased in linear fashion as the test progressed (Figs. 4 and 5). In

some, the degree of deviation rose to a peak and then decreased (Fig. 6). The latter sequence of events suggested that compensatory mechanisms in the circulation had brought about a favorable adjustment in coronary blood flow.[6] One of the methods of adaptation appeared to be an increase in pulmonary ventilation.[7] Several patients have given

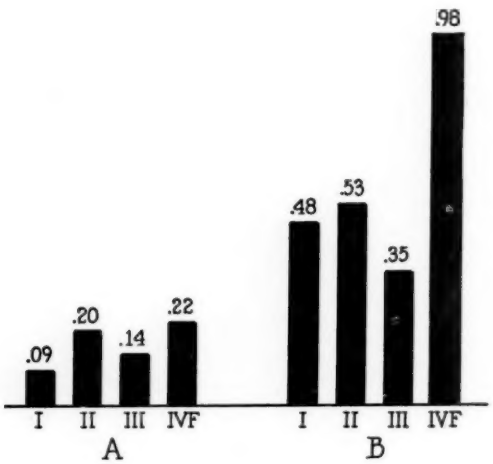

Fig. 3.—Average RS-T deviation which occurred in each lead during the anoxemia test. *A*, in the normal group; *B*, in the patients with coronary sclerosis.

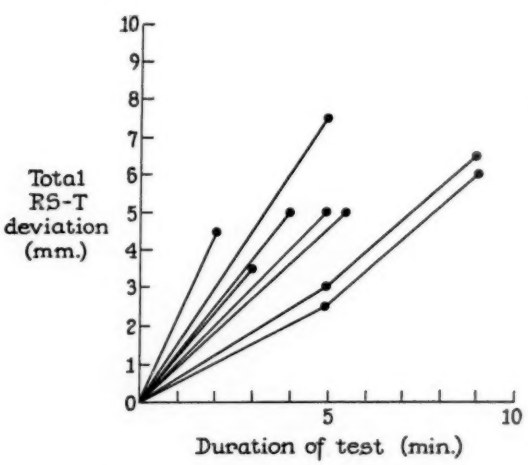

Fig. 4.—Marked RS-T deviation in eight tests on a patient with coronary sclerosis. Pain appeared during the first ten minutes. This man later died suddenly.

an account of their pain which makes it seem likely that similar adjustments take place on effort. One man stated that he had discomfort on beginning to walk, but that this wore off after he had "limbered up." He could then continue for an indefinite time, provided he did not hurry. A similar experience on the golf course was described by

another patient. While playing the first hole or two he was likely to have pain; thereafter, he could go on without being aware of his heart.

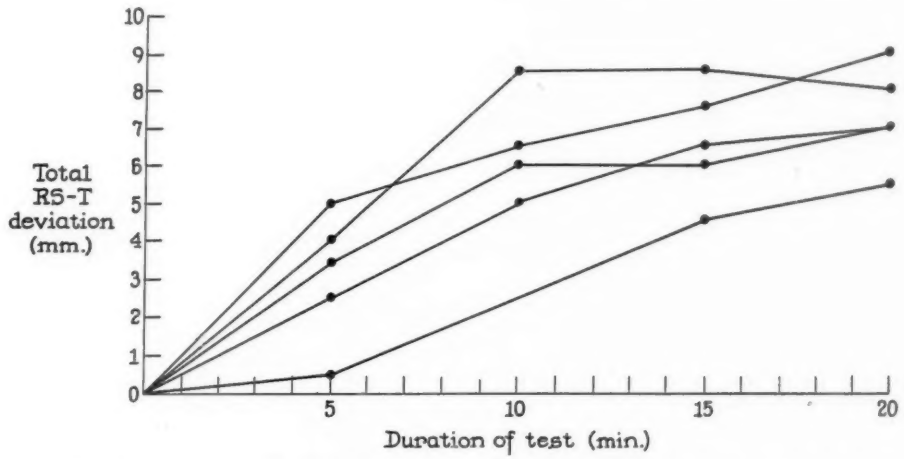

Fig. 5.—Marked RS-T deviation in five tests on a patient who never experienced pain during anoxemia. He later had an attack of coronary occlusion with cardiac infarction.

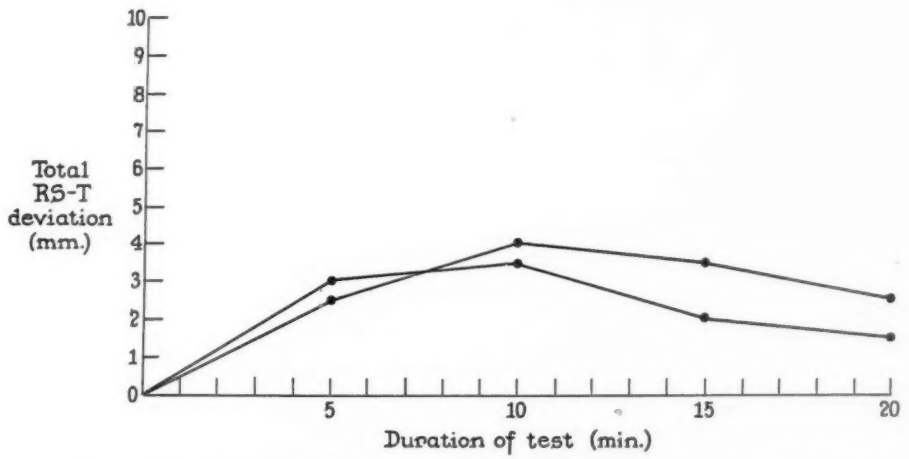

Fig. 6.—RS-T deviation in two patients with coronary sclerosis who did not experience pain during the test. There was apparent compensatory adjustment of the coronary circulation, as shown by the initial rise in the curve, followed by a fall.

In comparing the results on different patients with coronary sclerosis, no direct relationship could be demonstrated between the degree of RS-T deviation and the duration of the tests; patients who breathed the low-oxygen mixture for twenty minutes did not tend to show greater RS-T changes than those whose tests were terminated at the end of five or ten minutes because pain was felt (Fig. 7). In other words, the duration of the test did not determine the absolute magnitude of total RS-T deviation.

Age likewise did not affect the degree of RS-T deviation, either in normal subjects or in patients with coronary sclerosis.

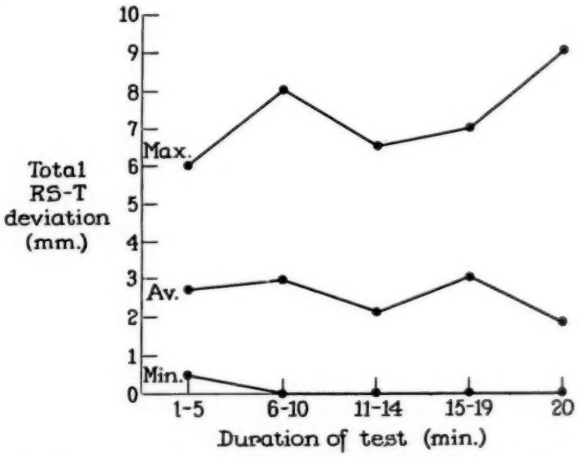

Fig. 7.—The maximum, average, and minimum total RS-T deviations in relation to the duration of the test in the group with coronary sclerosis.

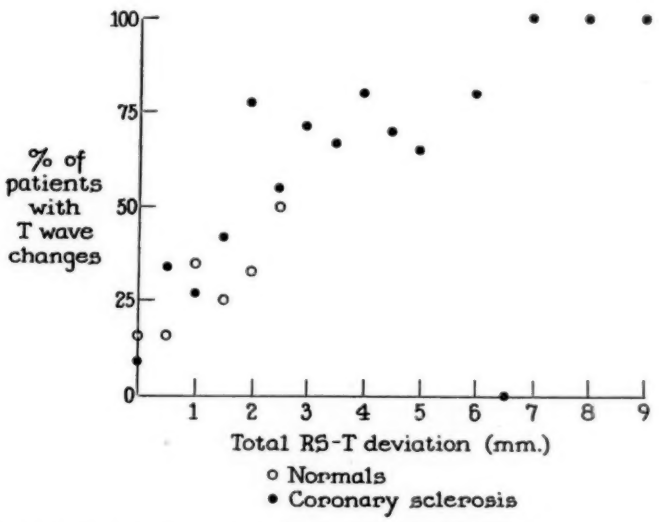

Fig. 8.—Percentage of normal and coronary patients who showed T-wave changes, in relation to the degree of RS-T deviation.

T-Wave Changes Alone.—By change in the T wave, partial or complete reversal in its direction is meant, whether this be from upright to inverted or the opposite. In both groups the incidence of such a change increased with the degree of total RS-T deviation (Fig. 8). There was one exception, in which a deviation of 6.5 mm. was unaccompanied by any change in the T waves. A comparison of the occurrence of T-wave changes in normal subjects and in patients with coronary sclerosis showed an almost equal percentage in Lead III, but, in

Leads I, II, and IVF, reversal of T was more often observed in the coronary group. The difference was most striking in Leads I and IVF (Fig. 9). In not a single normal person was the direction of T in IVF completely reversed, whereas in the coronary patients this was noted in twenty-three tests. Furthermore, in the coronary group, T-wave changes occurred in more than one lead in forty-five tests (28.6 per cent), whereas in the normal patients multiple changes were observed only five times (3.7 per cent).

Age did not affect the incidence of RS-T changes, either in normal patients or in the patients with coronary sclerosis.

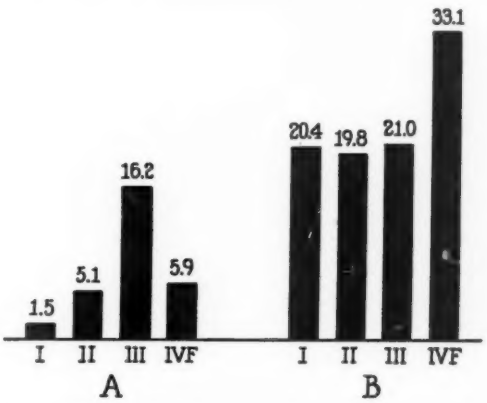

Fig. 9.—Percentage of subjects who showed partial or complete reversal in the direction of the T wave during the test. The figures for each lead are given separately. *A*, normal patients; *B*, coronary patients.

T-Wave Changes Associated With RS-T Deviations.—In the normal patients a change in the direction of the T wave never occurred in association with an RS-T deviation of 1 mm. or more. In the coronary group, on the other hand, this was observed in twenty-one cases. T in IVF was partially reversed, with an associated RS-T deviation of 1 mm. or more, in two normal subjects and in seventeen cases of coronary sclerosis. T_2 was partially or completely reversed, with an associated RS-T deviation of 1 mm. or more, in two tests on normal subjects and in sixteen patients in the coronary group. The same combined changes were noted with respect to T_3 twice in normal persons and ten times in coronary patients.

DISCUSSION

The usefulness of the anoxemia test depends primarily upon the validity of the criteria which distinguish a normal from an abnormal reaction. On the basis of previous experience, four types of change in the four-lead electrocardiogram which occur as the result of induced oxygen want have been described as indicative of a diminished coronary reserve.[2, 3] Examination of the results on the 136 normal subjects included in this study showed that, in two (1.4 per cent), there ap-

peared electrocardiographic changes which were heretofore regarded as evidence of coronary insufficiency. Both of these subjects were in the third decade of life. The changes observed were referred to as "criterion 4" in earlier papers, and consisted of partial reversal in the direction of the T wave in Lead IVF, accompanied by an RS-T deviation of 1 mm. or more in this lead. In the group of 157 coronary cases, the test was positive in seventy-seven (49 per cent), but in only three cases (1.8 per cent) was the test considered positive solely on the basis of this criterion. In all of the remaining cases, other criteria of a positive reaction were also present. It is thus apparent that the combination of partial T-wave reversal and an RS-T deviation of 1 mm. or more in the precordial lead occurs in a small number of persons with normal hearts; and that, as an isolated observation, it is rarely helpful in the recognition of coronary insufficiency. In this series of cases, it was noted with about equal frequency in normal subjects and in patients with coronary sclerosis. Accordingly, the use of criterion 4 has been discontinued. It is our present opinion that the test is positive when *any one* of the following is found:

1. The arithmetic sum of the RS-T deviations in all four leads (I, II, III, and IVF) totals 3 mm. or more.

2. There is partial or complete reversal of the direction of the T wave in Lead I, accompanied by an RS-T deviation of 1 mm., or more, in this lead.

3. There is complete reversal of the direction of the T wave in Lead IVF, regardless of any associated RS-T deviation in this lead.

Strong presumptive evidence of diminution in the coronary reserve is afforded by the occurrence of pain during a test which is electrocardiographically negative. The successful use of pain as an index will depend upon the observer's ability to differentiate it from the minor discomfort of an apprehensive subject, and his astuteness in detecting the occasional malingerer. A complaint of pain should not be considered presumptive evidence of a positive test when payment for disability insurance is involved.

SUMMARY

1. In 157 cases of coronary sclerosis, the anoxemia test was electrocardiographically positive in 49 per cent, and furnished presumptive evidence of coronary insufficiency, by the occurrence of pain, in another 20 per cent. It was thus helpful in the recognition of a diminished coronary reserve in 69 per cent.

2. The RS-T deviation in each individual lead, as well as the total RS-T deviation in the four leads which were employed, was greater in the 157 patients with coronary sclerosis than in 136 normal persons.

3. The amount of total RS-T deviation usually increased in linear fashion in relation to the duration of the period of anoxemia. Occa-

sionally the degree of deviation rose to a peak level and then decreased, suggesting that compensatory mechanisms operated to bring about a favorable adjustment in coronary blood flow.

4. Comparison of the results on different patients with coronary sclerosis showed no direct relationship between the duration of the test and the amount of total RS-T deviation; patients who breathed the low-oxygen mixture for twenty minutes did not tend to show greater RS-T deviation than those whose tests were terminated earlier because of pain.

5. The incidence of significant T-wave change increased with the degree of total RS-T deviation.

6. The combination of partial T-wave reversal and RS-T deviation of 1 mm. or more in Lead IVF, as the sole criterion of a positive test, was observed in less than 2 per cent of the cases of coronary sclerosis and was found with equal frequency in normal persons. Its use as a sign of a positive reaction has, therefore, been discontinued.

ADDENDUM

Since this paper was prepared for publication there has appeared an article by C. T. Burnett, M. G. Nims, and C. J. Josephson (The Induced Anoxemia Test: A Study by Age Groups, AM. HEART J. **23**: 306, 1942), in which the authors have expressed certain conclusions that are at variance with our experience. A number of the questions raised by their observations have been answered by the incisive comments of Dr. Douglas Deeds, of Denver, published in the same issue of the AMERICAN HEART JOURNAL (p. 334). A reply to others will be found in a recent paper and in the discussion which followed its presentation (Levy, R. L., Patterson, J. E., Clark, T. W., and Bruenn, H. G.: The Anoxemia Test as an Index of the Coronary Reserve: Serial Observations on One Hundred and Thirty-Seven Patients With Their Application to the Detection and Clinical Course of Coronary Insufficiency, J. A. M. A. **117**: 2113, 1941). Some of the reasons for disagreement are here briefly recapitulated.

1. The studies of Burnett and his associates were carried out in Denver at an altitude of 5,420 feet, where the average barometric pressure is 630 mm. of mercury; at sea level this pressure averages 760 mm. of mercury. Thus, a 10 per cent oxygen mixture in New York is approximately equivalent to an 8 per cent concentration of oxygen when transferred to one mile above sea level. In addition, in at least six cases, through an error, Burnett used a mixture containing 8.6 per cent of oxygen.

2. Breathing a 10 per cent oxygen mixture at sea level simulates atmospheric conditions at an altitude of approximately 18,000 feet. If the test is done at an elevation of 5,420 feet, the altitude equivalent during induced anoxemia is about 23,420 feet. The strain imposed on the circulation by the altitude is disproportionately greater as more

rarefied atmospheres are attained, so that the change from 18,000 to 23,000 feet represents a greater increment of increase than does the transition from 13,000 to 18,000 feet.

3. It is an assumption, unsupported by evidence, that persons in Denver, "acclimatized" to the altitude by long residence, react to induced anoxemia as do those who live and are tested at sea level.

4. In not a single person with a normal cardiovascular system have we observed pain during a test. Some of Burnett's subjects experienced pain; and in 19.2 per cent of clinically normal persons he found an abnormal response, according to our criteria. But his so-called "normal" subjects were evidently not very carefully chosen. For example, a 47-year-old man (Case 39) experienced discomfort both during the test and for some time afterward. He also showed an abnormal response according to all criteria. This result is qualified by the ingenuous statement that "we learned later that he had some hypertension, without other evidence of cardiovascular abnormality."

5. According to Burnett, a negative response "may further cloud the clinical picture." We have repeatedly stressed the point that only a positive test is significant. A negative Wassermann reaction does not exclude the presence of syphilis. The value of any test depends upon its intelligent interpretation.

In summary, the observations of Burnett and his collaborators, because of the conditions under which they were made, are not comparable to those reported by us. Their conclusions, therefore, cannot be regarded as applying to the results of the "anoxemia test" which we have described.

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THE RATIONALE OF OPERATIVE TREATMENT OF SUBACUTE BACTERIAL ENDARTERITIS SUPERIMPOSED ON PATENT DUCTUS ARTERIOSUS

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CIRCULATORY failure and subacute bacterial endarteritis, usually of the *Streptococcus viridans* variety, constitute the two most important complications of patent ductus arteriosus. Although Munro,[18] in 1907, apparently was the first to suggest that circulatory disturbance might be corrected by ligation of the ductus, it was not until 1939 that Gross and Hubbard[13] reported the first such successful procedure and thereby demonstrated the effectiveness of surgical therapy in correcting circulatory abnormality.

The first attempt at operative treatment of subacute *Streptococcus viridans* endarteritis superimposed on patent ductus arteriosus, was reported by Graybiel, Strieder and Boyer[11] in 1938. (This, incidentally, represented the first effort ever made to operate upon a patent ductus arteriosus.) At operation, the right branch of the pulmonary artery was so intimately adherent to the ductus that an attempt to separate the two structures from one another appeared extremely hazardous. Accordingly, an effort was made to obliterate the lumen of the ductus by introducing a series of external plicating sutures. Unfortunately the patient succumbed on the fourth postoperative day, of acute gastric dilatation. At autopsy, the ductus was found to have been only partially occluded. Vegetations were present in the pulmonary artery and at the pulmonic orifice of the ductus. The lungs contained many small scattered infarcts, a few of which had undergone central softening and necrosis.

After noting the post-mortem findings outlined above, Graybiel, Strieder, and Boyer concluded that cure could not have been achieved in their case by the procedure which had been attempted. In support of their contention, they pointed out that, even if ductal occlusion had been accomplished successfully, it would not have destroyed the vegetations which existed within the ductus, let alone those within the pulmonary artery. They stated that the only procedure which *might* prove successful in such a case, was one that would remove *all* vegetations from direct contact with the blood stream; and they indicated

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that such an operation would have to consist of obliteration not only of the ductus but also of the adjacent portions of the pulmonary artery. Subsequently, Gross[12] warned against operation in the presence of superimposed infection, and stated, "Subacute bacterial endocarditis must be regarded as a contraindication to operation because the friable vegetations around the ductal opening will almost certainly be dislodged and result in embolism or a more severe bacteremia."

Following the unsuccessful effort reported by Graybiel, Strieder, and Boyer, no attempt at operative treatment of subacute bacterial endarteritis superimposed on patent ductus arteriosus was recorded until 1940.* In June of that year, however, the author and Vesell presented four such cases before the annual meeting of The American Association for Thoracic Surgery.[27] The first patient recovered without benefit of chemotherapy and has remained entirely well up to the present time (more than two years since operation).[26] The second patient was unimproved (apparently because vegetations already were present upon the aortic valve) and died of the original subacute *Streptococcus viridans* infection about eight months later. The third and fourth patients succumbed of accidental hemorrhage during operation. In all four cases, the ductus was sclerotic, friable, and adherent to the pulmonary artery as in cases described by Abbott,[1] Graybiel, Strieder, and Boyer,[11] Hamilton and Abbott,[14] and Schlaepfer.[20]

In the following year, in an effort to reduce the difficulties and dangers of operation, the operative technique was modified;[22] and since then four additional patients suffering from relatively early infection, have been subjected to surgical treatment.† In these cases, operation consisted merely of division or ligation of the ductus without any attempt to perform the radical procedure which Graybiel, Strieder, and Boyer assumed to be a requisite of cure when vegetations exist in the pulmonary artery. Nevertheless, all four patients recovered promptly without benefit of chemotherapy.[24, 25, 28] Under the circumstances, it might be maintained that, since recovery ensued, vegetations were not present within the pulmonary artery. The investigations of Abbott[1] indicate, however, that in cases of infected patent ductus arteriosus, early involvement of the pulmonary artery is practically a constant finding. The latter was substantiated by the post-mortem findings, in the case reported by Graybiel, Strieder, and Boyer[11] and in two personal cases to which reference already has been made.[27] The duration of infection in these three cases varied between three and one-half and five months, and vegetations were found within the pulmonary artery in all.

*In July, 1940, Keele and Tubbs,[16] of London, reported a case of infected patent ductus in which the patient survived operation but was not cured of infection. Following intensive chemotherapy, the blood cultures finally became sterile, thirteen months postoperatively.[5]

†Two patients suffering from infection of long duration also have undergone operation. Since they fall within a special group, now under investigation, they are excluded from the present discussion.

In the author's five successful cases, the duration of infection varied between one and four months, and, although the interior of the pulmonary artery could not be inspected at operation, it seems warranted to assume that vegetations already were present within the lumen. Even if it were conceded, for purposes of discussion, that vegetations were not present within the pulmonary artery, all will agree that vegetations were present within the ductus. It also will be agreed that such vegetations could not have been removed completely from contact with the circulating blood, by so simple an operation as ductal ligation or division. Inasmuch as the latter procedures were followed by recovery, without benefit of chemotherapy, some explanation of their efficacy must be offered.

The author's theory of the mechanism of recovery, rests partly upon observations which are supported by clinical and laboratory data and partly upon assumptions for which only indirect evidence is available at present. It therefore is offered not as the only possible explanation of cure, but rather as a tentative hypothesis which appears to be best supported by the evidence at hand. Under the circumstances, it is quite likely that, in the light of future investigation and observations, the following viewpoint may require some modification.

PATHOLOGIC ANATOMY AND PHYSIOLOGY

In those instances in which patent ductus arteriosus is unassociated with other congenital cardiovascular abnormalities, such as subaortic or pulmonic stenosis, coarctation of the aorta, and septal defects, evidence has been presented by Eppinger, Burwell and Gross[9] to indicate that the direction of the hemic flow through the ductus is essentially from the aorta toward the pulmonary artery. This is assumed to be due to the fact that, throughout the cardiac cycle, the pressure of blood in the aorta is higher than in the pulmonary artery. The current, which swirls through the ductus and impinges upon the wall of the pulmonary artery opposite the orifice of the ductus, eventually produces thickening of the intima and atheromatous plaque formation within the ductus and pulmonary artery. According to Buchwald[6] and to Rokitansky,[10] such changes are most likely to be found at, or near, the pulmonic orifice of the ductus. When subacute bacterial infection supervenes, vegetations apparently develop chiefly upon these pre-existing sclerotic and atheromatous plaques.* *Thus, even early in the course of infection, vegetations usually are found not only in the ductus itself but in the pulmonary artery as well.* Abbott[1] has emphasized the frequency of early involvement of the pulmonary artery, by stating, "The pulmonary end of the ductus with the immediately adja-

*Allen[2] has presented evidence to indicate that the development and growth of vegetations is favored in areas which are subjected to mechanical "impact and contact" by the infected blood stream. In cases of patent ductus arteriosus, the wall of the ductus and the wall of the pulmonary artery (opposite the orifice of the ductus) constitute such areas of impact and contact, and it is there that infected vegetations develop most commonly.

cent tissues (pulmonary artery) is always the initial seat of the vegetative inflammatory lesion."

The author assumes that, once vegetations have become established in the ductus and pulmonary artery, they are subjected to the unceasing trauma of the swirling ductal current. It is postulated that, as a result of the continuous agitation of the vegetations, infected emboli and organisms are broken off and enter the circulation more or less uninterruptedly. Organisms and infected emboli, derived from vegetations within the ductus and pulmonary artery, can enter the peripheral circulation only through two routes. The first is through the ductus directly into the aorta. The second is through the pulmonary circuit, to the left side of the heart, and then into the aorta.

Hubbard, Emerson, and Green,[15] in addition to Abbott,[1] have stressed the fact that vegetations within the ductus are situated most commonly at or near the pulmonic orifice of the latter structure. In view of the direction, velocity, and constancy of the hemic current which swirls through the ductus, it appears logical to assume that most of the infective material which is derived from vegetations within the ductus is swept into the pulmonary artery. On the other hand, it is known that reverse eddy currents often exist along the edges of a swiftly flowing stream, and it is quite possible that in cases of infected patent ductus a certain amount of infective material may be carried into the aorta by such currents. It is further assumed that septic emboli and organisms derived from vegetations within the pulmonary artery are swept almost exclusively into the branches of the pulmonary arterial tree, for, in order to enter the aorta directly, it would be necessary for such material to pass through the ductus against the full force of the continuously onrushing ductal current.

In certain cases vegetations, in addition to being present near the pulmonic orifice, may be found close to the aortic orifice of the ductus. This is especially true when the ductus is short. It is postulated that, in such cases, infective material may be carried into the aorta fairly freely, by the eddy currents to which reference already has been made. In rarer instances, the "ductus" consists merely of a fistulous opening between the aorta and the contiguous pulmonary artery. In such cases, it appears quite likely that infective material is shed directly into both the pulmonary artery and aorta.

From all of the foregoing theoretical considerations, it is assumed that, in the majority of cases of infected patent ductus arteriosus, the major portion of infective material derived from vegetations within the ductus and pulmonary artery is carried into the pulmonary circuit and only a relatively small amount enters the aorta directly through the ductus. In certain less common situations, however (vide supra), significant quantities of such material are assumed to enter the aorta as well as the pulmonary artery.

Evidence in favor of the entry of infected emboli and organisms chiefly into the pulmonary circuit is afforded by the following clinical and laboratory observations: (1) Episodes of spontaneous pulmonary embolization are quite common, even early in the course of infection; (2) during the early stages of infection, peripheral embolization is uncommon; (3) at post-mortem examination, vegetations are found within the pulmonary artery in almost every instance, and upon the pulmonic valve frequently; (4) at post-mortem examination also, even in cases in which infection has been of long duration, vegetations rarely are found within the aorta. The author recently demonstrated, by taking blood cultures simultaneously from the surgically exposed pulmonary artery and aorta of a patient suffering from patent ductus arteriosus with superimposed infection, that very many more organisms were present in the pulmonary artery than in the aorta.[23] In the absence of a feeding focus in the peripheral circulation or right side of the heart, the latter findings could be attributed only to the direct entry of organisms, into the pulmonary artery, from vegetative lesions situated within the ductus or pulmonary artery, or both.

An argument in favor of the assumption that a certain number of organisms enter the aorta directly through the open ductus is to be found in the author's observations concerning the amazing rapidity with which the peripheral blood cultures become negative following operation in certain cases.[24-28] (This subject will be discussed in detail in a forthcoming communication.) In certain rare instances, the entry of large amounts of infective material directly into the aorta is suggested at post-mortem examination, by the presence of vegetations within the aorta at some distance from the aortic orifice of the ductus. It also is indicated in the rare case in which peripheral embolization is noted during life, without vegetations being found in the left side of the heart or aorta at autopsy.

Animal experimentation[3, 7, 8, 21, 29, 30] and the author's observations,[23] in a patient suffering from *Streptococcus viridans* sepsis (vide supra), indicate that large numbers of organisms which enter the pulmonary circuit are removed in the lungs. However, the fact that peripheral blood cultures remain positive during the course of asepsis indicates that some organisms pass through the pulmonary capillaries to gain access to the general circulation. In this connection it seems logical to assume that a condition such as patent ductus arteriosus, in which the pulmonary artery and its radicles are dilated, may result in further impairment of the already inadequate pulmonary protective mechanism.

In patent ductus arteriosus, dilatation of the pulmonary arterial tree is due to an increase in the pressure, volume, and rate of flow of blood in the pulmonary artery, resulting from the arteriovenous shunt. (Such dilatation is recognizable in the roentgen film by an increase in size of the pulmonary artery and its larger branches and also by the presence

of bilateral pulmonary vascular congestion.) The author postulates that the combination of increased pressure, volume, and rate of flow of blood in the pulmonary artery also serves to create a powerful driving force which tends to facilitate the passage of organisms through the dilated vascular channels of the lung. As was stated previously, such organisms enter the pulmonary arterial blood from vegetative foci situated within the ductus and pulmonary artery.

THE EFFECTS OF OPERATION

Ligation or division of the ductus serves merely *to close the abnormal communication* which exists between the aorta and pulmonary artery. *No vegetations are removed from the ductus or pulmonary artery.* Nevertheless in five patients, of the six who survived operation, recovery ensued without benefit of chemotherapy. As the result of observations made in the successful cases, the author is of the opinion that *sterilization* of the peripheral blood stream *precedes recovery* rather than follows it. This statement is based upon the fact that the peripheral blood cultures become sterile so promptly that it is inconceivable that the residual vegetations within the ductus and pulmonary artery could have healed* within so short a period of time (several minutes to several hours).

Surgical closure of a patent ductus arteriosus results in immediate restoration of the integrity of the aorta and pulmonary artery and in correction of the altered circulatory dynamics. As soon as the ductus is occluded, the forceful current which swirls from the aorta into the pulmonary artery is halted. The operation is assumed to produce three effects. (1) Vegetations within the ductus and pulmonary artery cease being violently traumatized. As a result, the dislodgment of infected emboli and organisms from these sources is greatly reduced. (2) Infective material, derived from vegetations situated on the pulmonic side of the ligature of the ductus, no longer can enter the aorta but must enter the pulmonary artery exclusively. (3) The pressure, volume, and rate of flow of blood in the pulmonary artery are restored to normal. This causes a disappearance of the powerful driving force, which formerly tended to facilitate the passage of infective material through the capillaries of the lung, and a prompt removal of the influences responsible for dilatation of the pulmonary artery and its branches (including presumably its finest radicles). Thus to summarize, it is postulated that closure of the arteriovenous shunt prevents the entry of organisms directly into the aorta, reduces the amount of infective material which is shed into the pulmonary circuit, and increases the efficiency of the pulmonary protective mechanism. As a result of the increase in efficiency of the pulmonary protective mechanism, relatively few organisms now are able to pass through the pulmonary capillaries to enter the peripheral circulation. Those which do enter apparently

*A detailed report of the postoperative blood cultures in these cases will be presented in a separate communication.

are removed effectively by the protective mechanism of the general circulation (reticuloendothelial system); the blood cultures thus become sterile. (Cases in which vegetations are situated on the aortic side of the ligature of the ductus, upon the cardiac valves, and within the aorta, will not be discussed here. However it is assumed that, in general, they will not respond satisfactorily to operation.)

Before complete recovery takes place, the residual vegetations in the ductus and pulmonary artery must undergo healing. That the latter may and does occur is demonstrated conclusively by the disappearance of all clinical manifestations and laboratory evidence of infection within a short time of operation. Healing of vegetations is assumed to take place either as the result of alteration of local mechanical factors or changes in nutrition, or perhaps both. According to the mechanical theories cited by Allen,[2] *Streptococcus viridans* vegetations develop at points which are subjected to excessive mechanical impact and contact by the infected hemic current. (In patent ductus arteriosus, the abnormal stresses and strains are maximal in the ductus and in the pulmonary artery at a point opposite the orifice of the ductus, and vegetations usually are present at those sites.) According to Friedman, Katz, and Howell,[10] fibrin is precipitated from the blood stream and vegetations develop at points of local stress and strain. Viable organisms, as a rule, are found only in the superficial portions of vegetations. It is assumed that these organisms remain viable, because they are protected from the phagocytic action of the blood stream by fibrin which is being precipitated continuously upon the surface of the vegetations. In accordance with the theory of the above-mentioned authors, it is postulated that operation, by eliminating the swirling current in the ductus, results in diminished deposition of fibrin upon the surface of vegetations situated within the ductus and pulmonary artery. The organisms, being no longer protected, are destroyed by phagocytosis; the vegetations then undergo involution.

The theory that operative closure of the ductus alters the nutrition of the residual vegetations is favored by Libman,[17] and by Boldero and Bedford.[4] It is well known that in subacute *Streptococcus viridans* endocarditis complicating chronic valvular disease, vegetations are found much more commonly in the left side of the heart than in the right. The authorities cited above, believe that the higher oxygen content of blood in the left side of the heart may be an important factor in favoring the growth of vegetations there. In accordance with this theory, they have postulated that in cases of patent ductus arteriosus complicated by subacute *Streptococcus viridans* infection the growth and perpetuation of vegetations in the ductus and pulmonary artery may be favored by the abnormally high oxygen content of the blood in the latter structures as the result of the arteriovenous shunt. Thus, when the shunt is closed surgically, these vegetations now lacking an oxygen supply adequate for their continued growth, tend to undergo involution.

SUMMARY AND CONCLUSIONS

Attention is called to the fact that involvement of the pulmonary artery by vegetations probably occurs at an early stage of infection concomitantly with the development of vegetations within the ductus itself.

It had been assumed previously by others that recovery could ensue in such cases only if operation were to consist of obliteration of the ductus and the involved adjacent portions of the pulmonary artery. Nevertheless, following simple division or ligation of the ductus, five of the author's patients recovered promptly without benefit of chemotherapy. Although the interior of the pulmonary artery could not be inspected at operation, it was assumed that vegetations were present.

The following explanation of recovery after the closure of infected patent ductus arteriosus, based upon certain assumptions and established facts, is offered tentatively. Vegetations develop within the ductus and pulmonary artery at the site of intimal thickenings and atheromatous plaques. The latter result from the trauma of the hemic current that swirls through the ductus and impinges upon the wall of the pulmonary artery opposite the orifice of the ductus. This current flows swiftly from the aorta toward the pulmonary artery, throughout the cardiac cycle, and continuously traumatizes the vegetations mentioned above. Infected emboli and organisms thereby are dislodged and, for the most part, are swept into the pulmonary circuit by the current in the ductus. Some organisms in all probability also enter the aorta through the ductus. In the presence of an open ductus, the pressure, volume, and rate of flow of blood in the pulmonary artery are increased. This results in dilatation of the pulmonary artery and all of its branches, including the finest capillaries, and also serves to create a powerful driving force which tends to facilitate the passage of organisms through the dilated pulmonary capillaries and into the peripheral circulation more freely than normally.

Ligation or division of the ductus serves merely to close the abnormal arteriovenous communication which exists between the aorta and pulmonary artery. At operation no vegetations are removed from the ductus or pulmonary artery.

The effectiveness of operation is explained as follows. As soon as the lumen of the ductus is obliterated, the swirling current in the ductus is halted abruptly, and its traumatizing action, upon vegetations within the ductus and pulmonary artery, ceases at once. As a result, the dislodgment of infective material into the circulation is greatly diminished. Infective material now can no longer enter the aorta through the ductus but must enter the pulmonary artery exclusively. At the same time, the factors responsible for dilatation of the pulmonary arterial tree are removed, and the driving force, which formerly tended to facilitate the passage of organisms through the dilated pulmonary

capillaries, disappears. This results in an increase in efficiency of the pulmonary protective mechanism. The relatively few organisms which pass through the pulmonary capillaries, to enter the peripheral circulation, now can be disposed of fairly readily by other protective forces of the body; the blood cultures usually become sterile within a short time.

Complete recovery occurs only after the residual vegetations within the ductus and pulmonary artery heal. Healing may be due to either alteration of local mechanical factors or nutrition of vegetations, induced by operation, and is indicated by early subsidence of clinical manifestations and laboratory evidence of infection.

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Department of Clinical Reports

SUBACUTE STREPTOCOCCUS VIRIDANS ENDARTERITIS SUPERIMPOSED ON PATENT DUCTUS ARTERIOSUS

Spontaneous Recovery. Recurrence After Twelve and One-Half Years. Recovery Following Operative Treatment.

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THE frequency with which subacute *Streptococcus viridans* infection becomes engrafted not only upon cardiac valves which have been previously damaged by disease but also upon pre-existing congenital defects of the heart, is too well known to require discussion. The occurrence of such infection in cases of patent ductus arteriosus constitutes one of the most common and serious complications of the latter condition. In this connection, only one case of spontaneous recovery from subacute *Streptococcus viridans* endarteritis superimposed on patent ductus arteriosus has been reported (Chester[1*]). Although the use of modern chemotherapeutic methods occasionally has been followed by recovery, the results of medical treatment in general have been disappointing, and infected patent ductus arteriosus still remains an almost invariably fatal disease.

During 1940, a more radical therapeutic approach to subacute *Streptococcus viridans* endarteritis superimposed on patent ductus arteriosus was made by one of us (A.S.W.T.) and Vesell,[4] and in that year we reported the first case in the literature in which surgical treatment proved successful.[3] (The patient remains entirely well, more than two years after operation.) A second patient, operated upon almost one year ago, likewise appears to have recovered completely.[5]

The case herein reported is of interest for several reasons. First, it represents only the second in the literature in which a patient with patent ductus arteriosus recovered *spontaneously* from superimposed subacute *Streptococcus viridans* infection. Apropos of this, although in Chester's case[1] the correctness of the clinical diagnosis of patent ductus

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*In Chester's case, the diagnosis of patent ductus arteriosus was based upon clinical and roentgenographic evidence; and the presence of the superimposed subacute *Streptococcus viridans* infection was established by positive blood cultures. After an illness which lasted for almost one and one-half years, the patient recovered spontaneously. When last observed, two years later, she was apparently entirely free of the superimposed infection.

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arteriosus is not to be questioned, final confirmation of the precise nature of the congenital cardiovascular anomaly, either by operative or post-mortem examination, is lacking. In the present case, the diagnosis of patent ductus arteriosus was confirmed at operation, when infection recurred twelve and one-half years after spontaneous recovery from an initial episode of subacute *Streptococcus viridans* infection. The case thus becomes the first in the literature in which spontaneous recovery from infection superimposed upon a *proved* patent ductus arteriosus, occurred. Second, it appears to be the only one to be reported, in which there was recurrence after recovery from an initial infection many years previously. Finally, the case is our third of recovery from infected patent ductus arteriosus following operative treatment.

REPORT OF CASE

History.—G. O., an English-born, white woman, aged 51 years, single, and a school teacher by occupation, was admitted to The Mount Sinai Hospital on Aug. 12, 1941. She was one of five siblings, none of whom was known to have had a congenital cardiac anomaly.* To the best of the patient's knowledge, she had not been a "blue baby." A cardiac murmur, attributed to a congenital anomaly, had been discovered early in adult life. She had had measles and pneumonia at 2, pneumonia at 14, and an operation for fistula-in-ano at 38 years of age.

Early in January, 1929, approximately twelve and one-half years before the present admission, the patient experienced lassitude, cough, and mild fever. The diagnosis of "grippe" was made. After an illness which lasted approximately one month, the symptoms ameliorated somewhat and she went to a nearby resort to recuperate. While there, weakness, lassitude, and cough again became marked. At the end of another two months, she suffered an episode of severe "pleuritic" pain in the right chest associated with dyspnea, bloody expectoration, shaking chill, and temperature of 105° F. Accordingly, she was admitted to the Atlantic City Hospital, under the care of Dr. I. Shenfeld. Shortly after admission, a blood culture was found to be positive for *Streptococcus viridans.* In view of the presence of the congenital cardiac lesion and the subsequent development of septic temperature, petechiae, and an enlarged spleen, several additional blood cultures were taken. When three such successive cultures were found to be positive, the diagnosis of subacute *Streptococcus viridans* endocarditis was made. During a three-month period of hospitalization, the temperature ranged from 98° to 99° and 102° to 104° daily, and new petechiae appeared. Splenic infarction and several episodes of pulmonary infarction also occurred. The treatment consisted of transfusions, supportive measures, and the administration of an autogenous vaccine obtained from organisms in the patient's blood. At the end of three months, she was discharged (July 15, 1929) with persisting low-grade fever.

During the next six months she was under the care of Dr. Daniel A. McAteer, of Brooklyn. During the first four of these months, the temperature ranged between normal and 101° F., and several blood cultures were positive for *Streptococcus viridans.* New petechiae appeared, and on one occasion the patient was said to have suffered an episode of renal infarction. However, during the last two months she became afebrile. (Throughout the six-month period, the treatment consisted only of

*The patient's first cousin, by consanguineous marriage, died of subacute *Streptococcus viridans* endocarditis superimposed on patent interauricular septum and pulmonic stenosis. The diagnosis was confirmed at post-mortem examination.

the use of supportive measures.) About fifteen months after the onset of illness, she apparently had recovered to such an extent as to be able to return to work. She then remained relatively well for approximately three years.

The patient first came under the observation of one of us (L.R.T.) early in 1934 and was then suffering from mild circulatory failure. At that time, her symptoms consisted of dyspnea on moderate exertion, orthopnea, and slight cough. In the ensuing seven years, these symptoms increased slowly; but during the six months preceding admission the dyspnea became considerably more pronounced.

Four and one-half weeks before the present admission to the hospital, the patient began to complain of weakness and cough. When she first sought advice, at the end of two weeks, the temperature was found to be 100.6° F. During the next two and one-half weeks she was observed at home; dry, hacking cough and fever continued. Five days before admission, she suffered a sudden severe attack of pain in the left side of the chest associated with hemoptysis. This was attributed to pulmonary embolism with infarction. Concomitantly the temperature rose and, during the next five days, ranged irregularly between 101° and 105° F. At the end of that period (on Aug. 12, 1941), she was admitted to The Mount Sinai Hospital with the provisional diagnosis of subacute bacterial endarteritis superimposed on patent ductus arteriosus.

Examination.—The patient was well nourished, but slightly sallow in appearance. She did not appear acutely or chronically ill. Temperature was 101.4° F.; pulse rate, 96; respirations, 20. Dyspnea and orthopnea were present. There was no cyanosis. No petechiae were seen, and there was no clubbing of the fingers; the fundi were negative. Examination of the heart revealed no obvious enlargement at the apex, but increased widening of the area of cardiac dullness was present at the base. A very loud, "machinery-like" murmur was heard over the pulmonic area, throughout systole and most of diastole. This murmur was transmitted upward into the root of the neck. It could be heard faintly over the medial border of the left scapula. The blood pressure was 105/60. Examination of the lungs disclosed impaired resonance, diminution of breath sounds, and the presence of fine and coarse râles at the left base posteriorly.

Laboratory Data.—A teleroentgenogram revealed the heart to be enlarged to the left. The pulmonary conus was prominent. Moderate pulmonary vascular congestion was present. There was some clouding at the left base. The urine was negative for albumin and sugar; microscopic examination failed to reveal red blood cells or casts. Examination of the blood disclosed 4,420,000 red cells per cubic millimeter and a hemoglobin content of 86 per cent. The white blood cells totaled 6,600 per cubic millimeter, with 61 per cent segmented polymorphonuclear cells, 10 per cent nonsegmented polymorphonuclear cells, 23 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophiles, and 1 per cent basophiles. A blood culture taken on the day of admission yielded forty colonies of *Streptococcus viridans* per cubic centimeter, after forty-eight hours' incubation.

Preoperative Course.—The administration of sulfapyridine was begun three days after admission. This was followed by a prompt but only temporary antipyretic effect. During the next six days, 31 Gm. of the drug were administered but then had to be discontinued because of the development of very severe nausea and vomiting. Five days later the administration of sulfathiazole was begun. This was continued for seven days without significant effect. A second blood culture, taken thirteen days after admission, disclosed the presence of fifty-two colonies of *Streptococcus viridans* per cubic centimeter. By the nineteenth hospital day, the hemoglobin content of the blood had fallen to sixty-two per cent and the patient's general physical condition had deteriorated considerably. Dr. Emanuel Libman saw her

in consultation at that time and, because of the general downhill course and the failure of chemotherapy to influence the infection, concurred in the opinion to proceed with surgical therapy. As in the two previous successful operative cases reported by one of us (A.S.W.T.), the relatively short duration of infection and the lack of evidence of valvular involvement and *peripheral* embolization appeared to render the case suitable for such treatment.

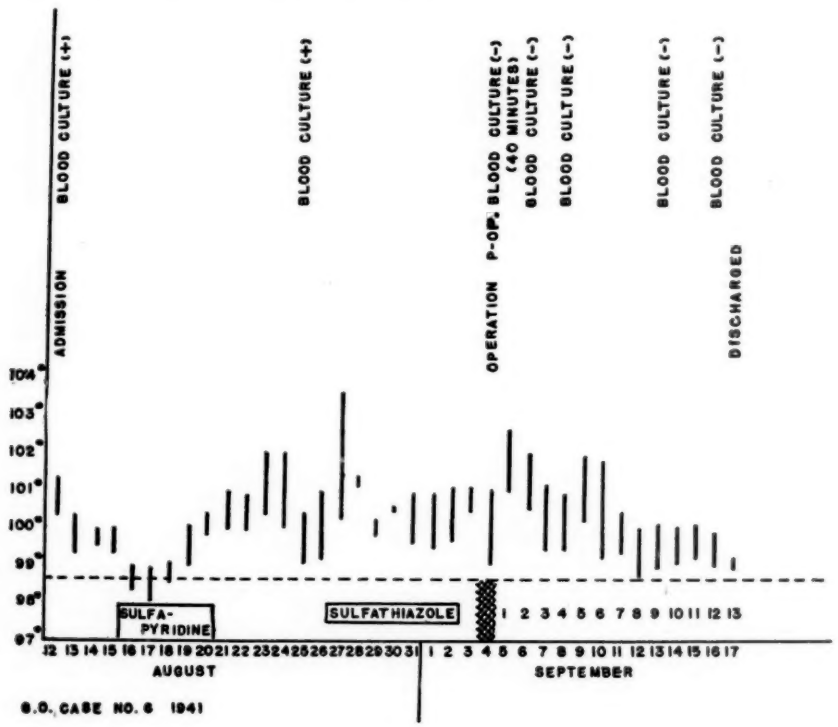

Fig. 1.

Operation.—On Sept. 4, 1941, twenty-three days after admission (or approximately eight weeks after the onset of infection), operation was performed (by A.S.W.T.) under avertin-ethylene anesthesia. The operative technique which was employed has been reported elsewhere[2] and therefore will not be described here. A brief description of the operative findings follows: Extensive adhesions were present between the lung and thoracic parieties, mediastinum, and pericardium. A visible tremor was noted over the base of the heart; a localized thrill was palpable over the region of the pulmonary artery. The aorta measured about 1 inch in diameter, and the pulmonary artery, about 1½ inches in diameter. Several inflamed lymph nodes and some edematous areolar tissue were present in the region between the undersurface of the aortic arch and the upper portion of the trunk of the pulmonary artery. The ductus measured approximately ⅜ inch long and ⅜ inch in diameter. When the ductus was compressed the thrill within the pulmonary artery and ductus ceased at once, the cardiac rate became appreciably slower, and the visible tremor of the heart disappeared. At the commencement of operation, the pulse rate was 102 and the blood pressure, 122/82. After double ligation of the ductus, the pulse rate was 86 and the blood pressure, 118/86. The duration of operation was fifty-five minutes.

Postoperative Course.—The postoperative course was relatively uneventful. The highest temperature recorded was 102.8° F. on the day following operation. Thereafter it receded, and after the eighth postoperative day it remained under the 100° level. By the thirteenth day the temperature was essentially normal. The cardiac murmur disappeared immediately after operation. The wound healed kindly, the skin clips being removed on the fourth postoperative day. Two days later, the silk retention sutures were removed and a small collection of serum was evacuated from the superficial wound. Serosanguineous fluid was aspirated from the left side of the chest on the third and fifth postoperative days, respectively. The patient was permitted out of bed on the ninth day and was discharged on the thirteenth day following operation.

The first postoperative blood culture was taken forty minutes after operation,* and the succeeding cultures, on the second, fourth, ninth, and twelfth postoperative days respectively. All remained sterile throughout fourteen days of incubation. *No chemotherapy was administered postoperatively.* At the time of discharge from the hospital the patient felt well, was gaining strength rapidly, and appeared to be in good physical condition. Since then she has improved progressively. At the present time, approximately nine months after operation, all evidence of circulatory failure has disappeared, and the clinical manifestations of infection remain absent.

SUMMARY

A 51-year-old female with patent ductus arteriosus, suffered an episode of subacute *Streptococcus viridans* endarteritis twelve and one-half years previously. At the time, the diagnosis of a congenital cardiac lesion was based upon the absence of a history of rheumatic fever and the presence of a characteristic murmur, known to be of long duration. The diagnosis of superimposed infection rested upon the presence of irregular fever, chills, malaise, splenic enlargement, petechiae, and several episodes of pulmonary infarction, and was confirmed by blood cultures which repeatedly were positive for *Streptococcus viridans.* The treatment consisted of repeated blood transfusions, supportive therapy, and injections of an autogenous vaccine. After an illness of approximately fifteen months, she apparently recovered completely.

The patient first came under the observation of one of the authors, with symptoms of mild circulatory failure, approximately eight years prior to the present admission. During the ensuing years the circulatory symptoms increased slowly but progressively. Approximately four and one-half weeks before admission to the hospital, clinical manifestations of superimposed infection, similar to those present twelve and one-half years previously, reappeared. During a twenty-three-day period of hospital observation, the clinical course was progressively downhill. The administration of both sulfapyridine and sulfathiazole was without significant effect; and blood cultures revealed as many as fifty-two colonies of *Streptococcus viridans* per cubic centimeter. Operation was performed primarily for the purpose of eliminating the infection. The procedure consisted of double ligation of the ductus, by a modification of technique devised by one of the authors. A blood culture taken

*The remarkable rapidity with which organisms disappear from the blood stream will be discussed in detail in a forthcoming communication.

forty minutes after operation was sterile throughout fourteen days of incubation. Four blood cultures were taken subsequently, and these likewise were negative. Chemotherapy was not administered during the postoperative course. Approximately nine months have elapsed since operation. All manifestations of infection and of circulatory failure remain absent, and the patient is in better health than in many years.

This is the first case of spontaneous recovery from subacute *Streptococcus viridans* infection superimposed upon a *proved* patent ductus arteriosus. It also is the first case of infected patent ductus in which, after recovery from an initial episode, the infection recurred. Finally, it is our third, in which operation upon a patent ductus arteriosus has been followed by recovery from infection.

The authors are greatly indebted to Dr. Shenfeld and Dr. McAteer, for information concerning the patient while she was under their care.

NOTE: Since this report was submitted for publication, three additional cases of infected patent ductus arteriosus have been operated upon successfully (by A.S. W.T.).

REFERENCES

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2. Touroff, A. S. W.: A Modified Technique of Surgical Ligation of Patent Ductus Arteriosus, Surgery (in press).
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4. Touroff, A. S. W., and Vesell, H.: Experiences in the Surgical Treatment of Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus, J. Thoracic Surg. 10: 59, 1940.
5. Touroff, A. S. W., Vesell, H., and Chasnoff, J.: Operative Cure of Subacute Streptococcus Viridans Endartetritis Superimposed On Patent Ductus Arteriosus. Report of the Second Successful Case, J. A. M. A. 118: 890, 1942.

Department of Reviews and Abstracts

Selected Abstracts

Corcoran, A. C., and Page, I. H.: Renal Blood Flow in Experimental Renal Hypertension. Am. J. Physiol. **135**: 361, 1942.

Hypertension due to renal arterial compression or compression of the renal parenchyma in perinephric scar may occur without constant or persistent changes in the renal clearances of diodrast, phenol red, inulin, or urea and without significant abnormalities of tubular excretory or reabsorptive capacity and, therefore, probably in the absence of ischemia of excretory renal tissue.

Measurements of total renal blood flow from the clearances and extraction percentages of phenol red and inulin indicate no correlation of mean arterial pressure with the rate of renal blood flow and establish the persistence of hypertension in the absence of renal ischemia. Evidence of renal vasoconstriction, predominantly of the efferent arterioles, was obtained from the levels of inulin extraction and renal blood flow in some dogs during phases of more severe hypertension and in association with secondary renal ischemia. In one dog in which hypertension was the result of perinephritis, intraglomerular filtration pressure was increased in the absence of changes in "effective renal blood flow." Ischemia due primarily to compression or occlusion of the renal artery was usually associated with decreased renal extraction of inulin, due apparently to decreased filtration pressure.

The persistence of experimental renal hypertension in the absence of renal ischemia is consistent with the view that intrarenal reduction of pulse pressure rather than ischemia may be the effective cause of experimental renal hypertension.

AUTHORS.

Heinbecker, P., and Barton, W. A.: An Effective Method for the Development of Collateral Circulation to the Myocardium. Ann. Surg. **114**: 186, 1941.

An effective method of producing a collateral circulation for the dog's myocardium is described.

The effectiveness is proved by the fact that, following complete ligation, at one operation, of the anterior descending and left circumflex branches of the left coronary artery approximately 1 cm. from the aorta, six of fourteen dogs survived. In control animals, such ligations were immediately fatal.

At autopsy the heart muscle of the surviving animals showed no gross infarction.

On the basis of the experimental evidence, it is felt that, for a maximally effective collateral circulation to the heart, the extrinsic source should contain blood vessels of large caliber.

The method should be applicable to the treatment of myocardial ischemia in man.

AUTHORS.

White, P. D., Adams, F. D., and Craib, D.: A Note on Cardiac Murmurs. Recommendation for a Revised Terminology. Am. J. M. Sc. 203: 52, 1942.

The true nature of the various types of murmurs is more clearly indicated by the following nomenclature:

Physiologic Murmurs.—A. Intracardiac or intravascular. B. Extracardiac. (a) Cardiopulmonary. (b) Pericardial.

Pathologic Murmurs.—A. Due to structural valvular disease. B. Due to congenital cardiovascular defects. C. Due to dilatation of ventricles or aorta or pulmonary artery from: (a) Cardiovascular disease. (b) Other diseases, such as anemia, thyrotoxicosis, or severe infection. D. Due to pericarditis.

AUTHORS.

Levin, E.: Action of Mercurial Diuretics on Blood Volume. Rev. argent. de cardiol. 8: 267, 1941.

Blood volume determinations were made in thirty-five patients with the Congo red method before and one or two hours after the administration of mercurial diuretics. Five of the eight nonedematous patients showed an increase of blood volume after the administration of diuretics; in four noncardiac edematous patients an even greater hypervolemia was detected. On the other hand, hypervolemia was seen in only a few of the cardiac edematous patients, most of them showing iso- or hypovolemia. The patients who had hypovolemia after the administration of diuretics had been previously digitalized.

The author suggests the advisability of previous digitalization to prevent the hypervolemia which might occur after the administration of mercurial diuretics.

AUTHOR.

Levine, S. A.: Auscultation of the Heart. New England J. Med. 225: 526, 1941.

Even a simple and time-honored custom and diagnostic procedure is subject to review and criticism in order to restate its principles, its practices, the interpretation of findings, and its value. Bedside medical physical diagnosis remains still an important part of cardiology and auscultation as one of the methods. The author treats the subject simply, and the article is good reading.

MCCULLOCH.

Burton, S. D., and Mehlman, J. S.: An Unusual P-Wave in Chest Lead CF_2 Following Spontaneous Pneumothorax. J. Lab. & Clin. Med. 27: 465, 1942.

A case is presented showing an unusual and deeply inverted P wave of 14 mm. in Lead CF_2. This P wave was produced by cardiac displacement, resulting from a spontaneous pneumothorax which brought the right auricle into close apposition to the anterior chest wall. The contour of the P wave was such as to suggest that the part of the auricle beneath the chest contained the pacemaker, the sinus node. As the pneumothorax was relieved, the large P wave became diphasic, suggesting the apposition of other parts of the auricle to the anterior chest wall. Finally, as further resolution of the pneumothorax progressed, the P wave returned to its smaller and more nearly normal appearance, which existed before the pneumothorax occurred. During the period of pneumothorax, the changes in the P wave with change in body posture indicated greater than normal mobility of the heart.

AUTHORS.

Evans, W.: Chest Lead (CR_1) Electrocardiograms in Auricular Fibrillation. Brit. Heart J. 3: 247, 1941.

The chest electrocardiogram, CR_1, was taken in sixty patients with auricular fibrillation in order to study the auricular wave. Large and conspicuous waves, resembling those of auricular flutter, were found in thirty-nine patients (Type I). In the remaining twenty-one cases (Type II) the auricular waves were small and no more conspicuous than in many limb lead electrocardiograms.

No factor was discovered that determined in a patient with auricular fibrillation whether the auricular movements would be represented in the CR_1 cardiogram by large or by small waves, except that, if the ventricular rate was high and the auricular oscillations were conspicuous in the limb lead cardiogram, distinct waves were likely to show in the CR_1 cardiogram. The etiology and the duration of the arrhythmia, the size of the right auricle, digitalization or its absence, and the thickness of the chest wall did not seem to decide whether a patient would exhibit large (Type I) or small (Type II) auricular waves.

The features of the auricular waves were clearly shown in those patients classified as Type I, and these were specially studied. The form of the waves, varying slightly in different patients, resembled the waves found in auricular flutter although they lacked the same constant pattern. The waves recurred continuously without a pause at the isoelectric level, and each showed a gradual upstroke followed by a steeper downstroke. The amplitude of the wave was occasionally subject to a natural variation, and this was independent of any known extrinsic factor, including respiration. Small waves were often bifid, thereby giving the appearance of two waves and explaining the more frequent oscillations seen in the limb lead cardiogram. The wave was no larger in mitral stenosis than in nonrheumatic auricular fibrillation.

The rhythm of the auricular waves was slightly irregular in eighteen patients, regular in thirteen except for interruptions by ventricular systole when the succeeding auricular wave was as often delayed as quickened, and quite regular in six cases, in which the rhythm was undisturbed even by ventricular systole, so that the tracing closely resembled that of auricular flutter.

The frequency of auricular waves in auricular fibrillation was found to be reasonably constant; the rate was 375 to 400 per minute in more than half the cases; with two exceptions the range was 350 to 450, and the average rate for all patients was 400. Higher rates of auricular contraction generally assigned to auricular fibrillation have been based on observations on limb lead cardiograms which often contain more than one oscillation representing a single beat of the chest lead cardiogram. The rate was uninfluenced by digitalis, but it was reduced by quinidine.

In two patients in whom a clinical diagnosis of auricular fibrillation was supported by a limb lead cardiogram, the CR_1 tracing demonstrated auricular flutter in one and 2:1 auriculoventricular block in the other. The value of this chest lead is also seen in elucidating cases of so-called impure flutter, better regarded as fibrillation, and in the interpretation of records with auricular waves in the limb lead cardiogram sometimes subdued or obscured, as in heart block and in paroxysmal tachycardia.

The chest CR_1 cardiogram permits the limited definition of auricular fibrillation as a succession of waves at the rate of about 400 per minute, differing slightly in size and shape, and with a rhythm which is regular almost as often as it is irregular. The ventricular responses in fibrillation have no constant relationship to the auricular waves, probably because the auricular rate is too high for any regular control.

In contrast auricular flutter shows a succession of waves at a rate of about 300 per minute, identical in size and shape, and perfect in rhythm. The ventricular responses in flutter are determined by the auricular waves giving a fixed or varying ratio.

AUTHOR.

Wearn, J. T.: Morphological and Functional Alterations of the Coronary Circulation. Bull. New York Acad. Med. **17**: 754, 1941. Harvey Lecture, New York Academy of Medicine.

The author reviews his work with the coronary vascular system during the past ten years. He presents an important recapitulation of this work and our present knowledge of the subject.

MCCULLOCH.

Green, C. A.: Observations on the Antistreptolysin O Titre in Relation to the Mechanism of Acute Rheumatic Fever. J. Path. & Bact. **53**: 223, 1941.

The antistreptolysin O titers of 1,346 sera from male adolescents, including various clinical groups and healthy subjects, have been determined.

The mean titer in normal controls was 79; in 82.3 per cent of the sera the titer was less than 125 units.

An increase in titer was invariably noted in scarlatina, the mean being raised to 300, with maximum titers occurring in the third and fourth weeks of infection.

Simple pharyngitis due to *Streptococcus haemolyticus* was usually but not always followed by a rise in titer, the mean being 263.

The mean titer in the active phase of acute rheumatism was 444 and during the inactive phase 210.

Of 110 attacks of acute rheumatism, 79.9 per cent were accompanied by a significant increase in titer which, in the majority of cases, reached maximum proportions at or just after the height of clinical activity; in 10.1 per cent of the attacks no change in titer was observed, and in 3.6 per cent the titers were reduced during the active phase.

Examples of the various types of antistreptolysin O response in rheumatic and nonrheumatic subjects are described.

AUTHOR.

Ragan, C., and Bordley, J., III: The Accuracy of Clinical Measurements of Arterial Blood Pressure, With a Note on the Auscultatory Gap. Bull. Johns Hopkins Hosp. **69**: 504, 1941.

The commonly employed clinical method of measuring blood pressure should not be looked upon as a truly accurate procedure. In most adult subjects it provides reasonably reliable information, but in a significant number of cases the information may be misleading. Misinformation is particularly likely to be obtained in subjects with unusually large or unusually small arms. If the arm is small, the clinical estimate of the systolic pressure is likely to be too low. If the arm is large, the clinical estimate of both systolic and diastolic pressure is likely to be too high. The error in either direction may exceed 30 mm. Hg.

The foregoing observations must be borne in mind whenever it is necessary to come to a decision concerning the diagnostic or prognostic significance of minor depressions or elevations in the level of the blood pressure.

Statistical studies of the relation between blood pressure and body weight should take into account the influence of the circumference of the arm upon the accuracy of the blood pressure measurements.

AUTHORS.

Friedman, M., Selzer, A., Kreutzmann, H., and Sampson, J. J.: The Changes in the Blood Pressure and in the Renal Blood Flow and Glomerular Filtration Rate of Hypertensive Patients Following Unilateral Nephrectomy. J. Clin. Investigation **21**: 19, 1942.

The total diodrast clearance was found to be reduced in four of five patients having unilateral kidney disease with hypertension. It was more reduced in the affected kidney than in the normal one. The total inulin clearance was diminished in two and normal in the remaining three patients.

The removal of the diseased kidney was followed by an increase in the renal blood flow and in the glomerular filtration rate of the remaining kidney in all five patients.

There was a significant blood pressure reduction in three of the five patients, but in none was there a complete return of the blood pressure to normal when last examined, despite the fact that in three of these patients there was no ischemia of the remaining kidney.

AUTHORS.

Goldblatt, H., Kahn, J. R., and Lewis, H. A.: Studies on Experimental Hypertension. XV. Experimental Observations on Hypertension Associated With Unilateral Renal Disease; Effect of Occlusion of the Ureter on Experimental Hypertension Due to Unilateral Renal Ischemia. Arch. Surg. **43**: 327, 1941.

Constriction of one main renal artery in the dog causes a variable rise of blood pressure, which persists for a variable period. Excision of the ischemic kidney results in a prompt fall of the blood pressure to normal. Similarly, in man, hypertension may be associated with unilateral renal disease, presumably producing ischemia, and removal of the diseased kidney results in a fall of the blood pressure to normal if the other kidney is normal.

Occlusion of one ureter in the dog does not result in elevation of blood pressure. Occlusion of the ureter performed at the same time that the main artery of the same kidney is constricted interferes with the development of the elevated blood pressure of a dog with unilateral renal ischemia. After the blood pressure has become elevated owing to constriction of one main renal artery, occlusion of the ureter of the same kidney causes a fall of blood pressure to normal within three to seven days. Constriction of both main renal arteries accompanied with occlusion of both ureters usually results in a moderate elevation of blood pressure, which persists until death of the animal in uremia. Occlusion of the ureter and constriction of the main artery of one kidney followed by contralateral nephrectomy also usually result in a moderate elevation of blood pressure, which persists until death occurs in uremia. A hypertensive effect is, therefore, produced by kidneys with the main artery constricted and the ureter occluded when no normal kidney is present.

A vasoconstrictor effect has been obtained (by the Läwen-Trendelenburg technique) with citrated plasma of the venous blood of kidneys with the renal artery constricted and the ureter occluded, although the blood pressure of the animals was not elevated. No vasoconstrictor effect, but rather a dilator effect, was obtained with the plasma of venous blood from the contralateral, normal kidney and with the plasma of systemic venous blood. This indicates that the effect of occlusion of the ureter on a kidney with the main artery constricted is not to abolish the production

of pressor substance but to interfere with the rate of entrance of pressor-producing substance from the kidney into the systemic circulation or diminish the amount produced. In either case, the failure of the blood pressure to become elevated as a result of the decreased amount of pressor-producing substance which enters the systemic circulation may also be due to the neutralizing effect of the contralateral normal kidney.

Although some human beings have already been described in whom excision of a kidney with the ureter completely obstructed or of a kidney from which no urine was obtained was followed by a return of the blood pressure to normal, the experiments indicate that this may not prove to be the rule and that in such cases excision of the kidney should be undertaken for the main purpose of removing the diseased organ rather than for possible cure of the hypertension. In all cases of contemplated unilateral nephrectomy it is desirable, with the limited means available at present, to determine that the other kidney is, as far as can be determined, normal, before removing an obviously diseased, though still functioning, kidney for the possible favorable effect of this procedure on the elevated blood pressure.

AUTHORS.

Glen, A. M. Temporary Vascular Occlusion Ending Fatally in Uremia. Brit. M. J. ii: 875, 1941.

This is a case of central dislocation of the hip with fracture of the pubic rami of the same side causing obstruction of the external iliac vessels. Relief of the obstruction by dividing the inguinal ligament was followed by sudden and profound collapse comparable to that resulting from the sudden release of a tourniquet left over-long in position.

Death resulted from uremia within four days of the accident, and the microscopic appearances of the kidneys corresponded closely with those recently described in cases of crush injury (Bywaters and Beall, 1941; Beall, Bywaters, Belsey, and Miles, 1941; Mayon-White and Solandt, 1941).

The hardness of the limb noticed after operation is interesting in view of the theory recently put forward by Patey and Robertson (1941) that the syndrome may be due to loss of substances from the circulation into the injured limb. Unfortunately no particular attention was paid to this aspect at the time.

It is hoped that the findings described may prove of interest to those investigating such cases and to others who may have to deal with similar injuries.

AUTHOR.

Felsen, J.: Intestinal Vascular Sclerosis. J. Lab. & Clin. Med. 27: 576, 1942.

The association of intestinal vascular sclerosis with long-standing hypertension is quite constant. In the reviewing of 1,000 necropsies at the Bronx Hospital from the standpoint of concomitant intestinal vascular sclerosis and generalized arteriosclerosis in the same person, agreement was found in all instances where advanced changes were present in the larger vessels.

Intestinal vascular sclerosis is essentially a disease of old age. The chief symptoms are distention, constipation, indigestion, and abdominal cramps. Therapy consists of cardiovascular supportive measures, an easily assimilated diet, intestinal aspiration, and intestinal oxygenation.

AUTHOR.

Bauer, G.: Venous Thrombosis: Early Diagnosis With the Aid of Phlebography and Abortive Treatment With Heparin. Arch. Surg. **43**: 462, 1941.

For successfully combating thromboembolic disease two measures are necessary—early diagnosis and immediate energetic treatment with heparin.

Phlebography permits of an earlier diagnosis than any other known method. With its aid the first manifestations of the disease in the lower part of the leg can be revealed.

If in this stage regular treatment with heparin is started, almost ideal results can be expected, for the whole disease often takes an abortive course.

In twenty-one cases in which the diagnosis of an early stage of thrombosis in the lower part of the leg was confirmed by phlebographic examination, the patients were treated with heparin, 100 mg. three times daily for three to five days. All of the patients recovered and were ambulatory within a few days.

In thirty-two similar cases in which treatment with heparin was not used, two patients died, three had pulmonary embolism, eight had pulmonary infarct, and in twenty-four the thrombosis spread to the femoral veins. The average length of confinement to bed was forty-three days.

AUTHOR.

Marvin, H. M.: Newer Surgery of the Heart and Large Vessels: Medical Aspects. Bull. New York Acad. Med. **17**: 737, 1941.

The author believes that, of the operations mentioned, those designed to provide the heart with a new source of blood are probably valueless. Surgical ligation of the patent ductus arteriosus seems destined to be of great importance in a group of patients that will probably always be numerically small. Total thyroidectomy may have a limited place, but in the absence of an elevated basal metabolic rate the indications for it are not very clear and the results are apt to be unsatisfactory. Alcohol injections into the thoracic sympathetic ganglia have been proved to be highly satisfactory by years of experience. The Brauer operation for adhesive mediastinopericarditis seems to me to be of demonstrated value in a few cases, and I believe the time has not come to discard it. Pericardiectomy for constrictive pericarditis may be confidently regarded as a major therapeutic procedure and a brilliant surgical contribution.

AUTHOR.

Fine, J., and Sears, J. B.: The Prophylaxis of Pulmonary Embolism by Division of the Femoral Vein. Ann. Surg. **114**: 801, 1941.

Thrombosis of the deep veins of the lower leg is the focus of the origin of the great majority of pulmonary emboli.

Pulmonary embolism until recently has been regarded as a dramatic postoperative catastrophe for which adequate prophylactic or therapeutic measures are not available. This is no longer tenable except in the case of massive embolus which has occurred in the absence of detectable signs of venous thrombosis of the lower leg and in the absence of a previous episode of embolism.

If the surgeon will conscientiously observe the patient from the very beginning and throughout the postoperative period for the signs and symptoms of phlebitis in the deep veins of the lower leg, he is likely to discover the existence of at least suspicious evidence of phlebitis in a much larger number of instances than heretofore in advance of the discharge of an embolus.

If the evidence of phlebitis in the lower leg is clear-cut, immediate division of the femoral vein below or above the profunda should be done (bilaterally if both legs are

involved). If embolism has not yet occurred, the procedure may be considered a justifiable prophylactic measure. If an embolus has been discharged, however massive it may be, so long as it is not fatal, immediate division of the femoral vein is the one most effective measure remaining to prevent the discharge from its commonest source of still another embolus which may prove fatal.

If the evidence of phlebitis is only presumptive, a decision can be reached by the venographic technique of Bauer.

If embolism has occurred in the total absence of signs or symptoms of phlebitis, the process will usually be demonstrated and lateralized by the venographic technique of Bauer. An embolus henceforth can be assumed to have arisen from the pelvic or other inaccessible veins only when no involvement of the deep veins of either lower extremity is shown to exist by employment of this technique.

There is no good evidence that division of the femoral vein involves any significant immediate risk or adds to the disability created by the phlebitis itself. On the contrary, aside from its prophylactic value for embolism, division appears to exert a favorable influence on the course of the disease probably because of the concomitant disruption of some of the pathways involved in the accompanying vasospastic reflexes.

Because pulmonary infarcts and fatal pulmonary embolism due to phlebitis of the lower leg occur frequently in nonsurgical as well as surgical patients, the therapeutic problems involved become the common concern of the internist as well as the surgeon.

AUTHORS.

Jackson, B., and Wald, G.: Action of Thiamine and Cocarboxylase on Frog Ventricle. Am. J. Physiol. **135**: 464, 1942.

Experiments are reported upon the action of thiamine (vitamin B_1) and of its pyrophosphate ester (cocarboxylase) upon the Straub preparation of the frog heart. This is a ventricular preparation, in which test solutions act directly upon the heart muscle and produce changes only in the amplitude of the beat.

Between pH 6.0 and 5.2 thiamine 10^{-3} by weight progressively depresses the beat to a complete stoppage. At a concentration of 10^{-4} this effect is still observed; at 10^{-5} it has become negligible. Cocarboxylase 10^{-3} behaves similarly but continues to depress the beat 10 to 25 per cent up to pH 7.6.

This action is independent of that of acetylcholine. Atropine, which completely abolishes the latter, has no effect upon the former. Further, the depressions produced by thiamine or cocarboxylase and by acetylcholine are simply and accurately summated when both types of substances are applied to the heart simultaneously.

Above pH about 6.0 thiamine 10^{-5} to 10^{-3} progressively antagonizes the action of acetylcholine. This effect is not exhibited by cocarboxylase. Depression of the heartbeat and acetylcholine antagonism therefore appear in these experiments under mutually exclusive conditions; thiamine shifts from the first to the second type of activity at pH about 6, while cocarboxylase, which depresses the beat at all pH's investigated, does not antagonize acetylcholine at all. The shift in behavior of thiamine with pH may be related to its change from a monoacidic to a diacidic base at pH's below 6. The significance of these effects in the intact animal cannot yet be evaluated.

AUTHORS.

Lowe, T. E.: Blood Pressure Changes Following Localized Myocardial Death. M. J. Australia **11**: 447, 1941.

It is possible to produce localized areas of necrosis in cardiac muscle, at predetermined sites and of controlled extent, by the injection of small amounts of concentrated phenol solutions.

These observations show that the destruction of localized areas of cardiac muscle, of the sizes indicated, produces no permanent disturbance of systemic blood pressure immediately after destruction, irrespective of the particular muscle bundle involved.

These experiments yield no clue to the causal factors of the fall of blood pressure observed, at least in later periods, by clinicians and experimental workers.

AUTHOR.

Cuykendall, M.: The Incidence of Heart Disease in the University Student Age Group. New York State J. Med. 41: 2037, 1941.

In the university student age group the rheumatic state has already produced anatomic change in practically all hearts susceptible to this change, but the syphilitic and degenerate heart diseases of middle life have not yet occurred. A survey of the incidence of heart disease was conducted among the 6,489 students in attendance at Cornell University during the academic year in 1938 to 1939.

In previous surveys wide variations in the incidence of heart disease result from lack of uniformity in the compilation of material. Some surveys include one or more of the various subheadings of etiological or physiologic diagnosis. Further variation in the reported incidence is due to confusion in the differentiation of the systolic murmur. In the present survey the anatomic diagnosis is considered to be the only diagnosis of organic disease. However, certain of the etiological and physiologic diagnoses with their incidence among Cornell University students are briefly noted so as to make possible a comparison with those surveys which include these additional conditions.

Organic heart disease was diagnosed in 1.5 per cent of the Cornell students, i.e., 1.10 per cent of the men and 3.0 per cent of the women. The rheumatic type of heart disease comprised 82 per cent of the organic heart disease in this group and was present in 1.2 per cent of the students. The mitral valve was involved in 90 per cent of the rheumatic hearts. Rheumatic heart disease was present in 2.6 per cent of the women and 0.8 per cent of the men students, a sex incidence ratio of 3:1.

Rheumatic heart disease is the most common type of heart disease present among the Cornell University students. Factors that are known to influence rheumatic heart disease—namely, age, sex, economic environment, prevalence of the rheumatic state in the community, and race—are found in general to exert the expected influence. An exception, however, is the influence of sex; the ratio of three times as much rheumatic heart disease among the women students as among the men is much greater than in any previously reported survey.

AUTHOR.

Keys, A., and Violante, A.: The Cardio-Circulatory Effects in Man of Neosynephrin (1-α-Hydroxy-β-Methylamino-3-Hydroxy-Ethylbenzene Hydrochloride). J. Clin. Investigation 21: 1, 1942.

The threshold dosage of neosynephrin in the average adult is about 2 mg. subcutaneously, 0.4 mg. intravenously, and 50 mg. orally. The threshold effect is a decline in pulse rate and usually a slight increase in blood pressure.

The average dosage of neosynephrin for satisfactory pressor and cardiac effect is about 5 mg. subcutaneously, 0.8 mg. intravenously, or 250 mg. orally. With these dosages the pulse rate declines 15 to 35 beats per minute, the systolic blood pressure rises 15 to 40 mm., and the diastolic blood pressure rises 10 to 30 mm.

The upper limit for safe and comfortable dosage of neosynephrin in normal adults is about 10 mg. subcutaneously, 1.5 mg. intravenously, and 300 mg. orally.

With rare exceptions no sensation or symptoms other than pilomotor excitation are elicited by dosages below these levels.

Neosynephrin increases the positivity of the T wave, decreases that of the P, and prolongs the diastolic pause; otherwise the electrocardiogram is essentially unchanged. Cardiac irregularities, extrasystoles, and escape phenomena do not occur except in rare cases with the largest doses.

Neosynephrin produces an increase in the size of the heart in both diastole and systole. The stroke output of the heart is increased, but the minute output of the heart is generally somewhat decreased. There is a slight prolongation of the circulation time and a slight increase in venous pressure. The total work of the heart is increased.

In the atropinized subject the pressor effect of neosynephrin is augmented and tachycardia is produced. The same result is obtained in vagotomized animals and in the isolated or denervated heart.

Tachycardia of sinus origin is readily controlled with neosynephrin, but tachycardia of ventricular or supraventricular origin is not affected. Sinus bradycardia responds to neosynephrin with a further decrease in pulse rate.

Neosynephrin differs from epinephrine in its small pressor and cardiac potency, its longer duration of action, and its stimulatory effect on some of the parasympathetic effectors, notably those of the cardiac vagus.

AUTHORS.

Dauber, D., Landowne, M., Katz, L. N., and Weinberg, H.: Effects of Interrupting and Restoring the Circulation to the Lower Extremities. J. Clin. Investigation **21**: 47, 1942.

The phenomena associated with the application and release of constricting tourniquets were observed.

Cardiac acceleration followed release of occluding cuffs about the lower extremities in normal subjects. This was absent or reduced in patients with thromboangiitis obliterans.

A fall in the blood pressure was caused by the opening of a temporary low-resistance pathway for blood through the dilated vessels resulting from the previous occlusion of the limbs.

Evidence is cited to prove that the primary mechanism inducing the cardiac acceleration is a reflex response to the drop in pressure in the central arteries (Marey's law).

The evidence presented also indicates that the cardiac acceleration is not caused by a metabolite accumulating in the constricted extremities and that it is not satisfied by the assumption that the reflex arises from the occluded vessel or from the tissue of the extremity.

AUTHORS.

Book Reviews

PRE-ECLAMPTIC AND ECLAMPTIC TOXEMIA OF PREGNANCY: By Lewis Dexter, A.B., M.D., Soma Weiss, A.B., M.D., and Collaborators. Little, Brown & Co., Boston, Mass., 1941, 415 pages.

There is some evidence that as pregnancy advances the blood pressure tends to increase. If this increase exceeds normal limits it is called pre-eclampsia. In all demonstrable respects, pre-eclampsia resembles essential hypertension, except that it occurs with pregnancy, in most cases disappears after delivery, and is often associated with, or preceded by, water retention. This feature may be part of the pregnancy, which tends to be associated with water retention, also without increase of blood pressure. In women who have had increased blood pressure during pregnancy, the incidence of cardiovascular renal disease in later life is greater than normal. Among middle-aged women with hypertension the incidence of hypertension during past pregnancies is greater than normal. If a woman has increased blood pressure during one pregnancy, her chances of having elevated blood pressure during a subsequent pregnancy are increased, although this may not happen.

There is also some evidence that patients whose blood pressure is increased during pregnancy show a greater than normal incidence of hypertension in their families and a tendency to constitutional features which are often associated with hypertension. These are statistical studies showing merely a trend. There remain many women who have increased blood pressure during pregnancy, but show no other evidence indicating a constitutional predisposition to hypertension.

When patients with essential hypertension become pregnant, the blood pressure may remain unaffected or increase, or, in a few cases, return to normal and remain there for the duration of the pregnancy, to rise again after delivery. Thus, the effect of pregnancy on pre-established hypertension is unpredictable.

There is, then, a relation between the increase of blood pressure in pregnancy and essential hypertension, but all attempts to define this relation have so far failed. Four general factors which must be considered are (1) the patient, apart from any constitutional tendency she may have toward an increase in blood pressure, (2) a specific factor in the patient predisposing her to increase in blood pressure (''hypertensive diathesis''), (3) the pregnancy, apart from any specific blood pressure raising factor, and (4) a specific blood pressure increasing factor of pregnancy.

Any attempt to explain the increase of blood pressure during pregnancy must fall into one of three groups.

Group I.—Factor 4 appears as a complication of pregnancy, irrespective of the patient's susceptibility to hypertension (Factor 1). This explanation ignores all the facts mentioned above, except the one that the blood pressure may rise during pregnancy in a patient who manifests no other evidence of a hypertensive diathesis. This, however, does not rule out its presence.

Group II.—Normal pregnancy activates or accentuates hypertension in patients predisposed thereto (Factor 3 and Factor 2). This explanation fits most cases but ignores (1) those in which an already elevated blood pressure is not further raised,

and (2) the fact that increased blood pressure in one pregnancy may be followed by normal blood pressure in a subsequent one.

Group III.—A specific, blood pressure raising factor (Factor 4) in pregnancy acts in persons who have a latent or demonstrable tendency to hypertension (Factor 2). This explanation conforms, I believe, to all the established facts, and practically covers the authors' thesis that toxemia of pregnancy is a *condition sui genereris* (p. 8), but that it occurs more easily in those who have a constitutional predisposition (p. 297).

Beyond this the authors become increasingly speculative. Because the manifestations of toxemia often persist if the ovum is retained in the uterus after the fetus has died, they believe that the placenta must (or may?) be responsible for their persistence, but, in spite of diligent search both by experiment and in the literature, they fail to suggest any substance or mechanism which could explain this function.

Their hypothesis is further weakened by the fact that they must assume the probability of a second missing link, for there is no evidence that any placental secretion directly affects the blood pressure. The authors thoroughly investigate all possible mechanisms whereby the blood pressure may be raised. The many observations on hepatic changes during pregnancy and the evidence that an antidiuretic substance may cause water retention and edema of some vital structures (perhaps parts of the brain) are interesting. In such cases an increase in blood pressure might be a compensatory mechanism.

Apparently, the authors would consider these the high lights of their book, but in addition they have reported a number of largely negative, original researches on the pressor substances in the pituitary gland, in the placenta, and on other hormones. These are also a complete clinical and pathologic discourse on the known facts of toxemia of pregnancy, and a chapter on the treatment in which they, naturally, lean heavily on the authority of Stroganoff and of Dieckmann and on the established routines of the Boston Lying-in Hospital.

The book constitutes an important contribution to the subject of toxemia, but it lays itself open to many criticisms which should not be necessary. It is poorly arranged, and its purpose is not immediately obvious. After a few introductory chapters the reader is detoured through a number of chapters which are given disproportionate prominence, apparently because they constitute the authors' original research contributions. Then follows the chapter on pre-eclamptic and eclamptic toxemia which is the purpose of the book. This chapter is without proper subdivisions or equivalent headings. Too often the authors disregard English syntax. However, the book is well printed and contains remarkably few misprints.

JULIUS JENSEN.

ANOXIA; ITS EFFECT ON THE BODY: By Edward J. Van Liere, Ph.D., M.D., Professor of Physiology, West Virginia University. University of Chicago Press, 1942, 269 pages, 17 illustrations, $3.00.

This is a review of the effects of anoxia, produced chiefly by high altitude or chamber experiments, on the physiologic functions of men and animals. It is timely and of direct importance to those who are working in aviation medicine. The book does not purport to cover the entire field of anoxemia in disease, but it will interest practicing physicians because it reviews our knowledge of the physiologic processes which are fundamental to a proper understanding of many of the phenomena of cardiac and pulmonary disease.

ISAAC STARR.

THE AUTONOMIC NERVOUS SYSTEM; ANATOMY, PHYSIOLOGY, AND SURGICAL APPLICATION: By James C. White, M.D., Assistant Professor and Tutor in Surgery, and Reginald H. Smithwick, M.D., Instructor in Surgery, Harvard Medical School. The Macmillan Company, 1941, second edition, 469 pages, 92 illustrations, $6.75.

This book is an outstanding and complete treatise on the autonomic nervous system. The presentation is clear, written in easy style, and brought up to the minute. The various aspects of the subject are treated in sufficient detail and with authority that would satisfy the critical and informed reader, and yet the book is excellently suited to the needs of the student. Part I, which comprises a little over a third of the book, is devoted to anatomy, physiology, drugs and hormones, and methods of study. Part II is devoted to the application of basic facts toward the understanding and treatment of diseases and syndromes that have some relation to the autonomic system. Part III gives a clear description of surgical techniques.

Statements are abundantly supported by authorities and complete bibliographies without breaking the sequence of description or making the reading laborious.

Older theories are refreshingly challenged in the light of new data, particularly in reference to the role of the autonomics in pain syndromes.

One of the authors (White), in discussing the transmission of visceral pain in the spinal cord (p. 142), states that it is likely that fibers which transmit such pain ascend, at least in part, in the posterior columns. This conclusion is based on the fact that, in some cases, chordotomy did not abolish the pain of bladder and colon distension. This has not been my experience in the study of over 100 chordotomies. My results indicate that the modality of pain, from whatever source, is mediated through the anterolateral column.

In discussing Raynaud's disease, the authors adhere to Raynaud's original contention that the disease is primarily an abnormality of the sympathetic system, but some very convincing evidence that Raynaud's disease is primarily a vascular abnormality has recently been presented. Lewis was the first to adduce such evidence, and is given credit. Dr. Julius Wolkin and I have recently obtained further evidence (AM. HEART J. 23: 535, 1942) that supports Lewis' contention. This is an important controversy because it implicates other diseases for which the sympathetics have been indicted on grounds that should be questioned.

The subject of essential hypertension is reviewed, and a fair appraisal given of the various surgical methods of treatment which are used at the present time. The authors endorse sympathectomy in the treatment of hypertension in selected cases; their own results have been quite favorable in groups I and II. They feel that bilateral excision of the sympathetic trunks from T_9 to at least L_1, together with both great splanchnic nerves from the semilunar ganglia to the mid-thoracic level, is the surgical treatment of choice.

The book is obviously the result of a painstaking and thorough digest of the literature by skillful critics who have themselves engaged phases of the subject in significant researches and clinical application.

OLAN R. HYNDMAN.

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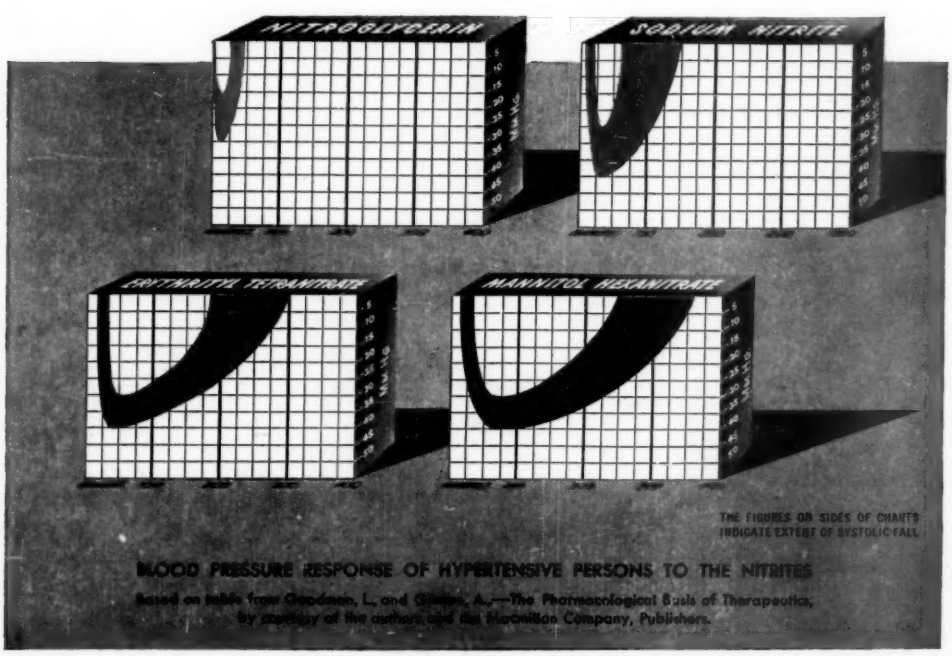

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